Genomics, Ethical Issues in

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Abstract

Improvements in our ability to analyze and understand DNA will have ethical implications for society. The most important issue stem from DNA's ability to predict an individual's future, during his or her life, at birth, as a fetus, as an *in vitro* embryo, or even before conception. There will also be ramifications for health care, in establishing identity, in revealing the past, through genetic manipulation, on ownership and control of genetic material and information, and in cultural understandings of humanness, race, and the roles of nature and nurture.

Genetics, both as a field and as a word, was born in the early twentieth century. The 'new' genetics referred to the vast increase in the power of genetics that followed the increased understanding of the biochemical basis for genetics in deoxyribonucleic acid (DNA). That understanding has made it possible to 'read' the sequence of DNA in organisms, including humans; to discover, in some cases, the physiological significance of that sequence; and to contemplate changing the sequence in order to attain desired ends. These heightened powers have both created new ethical and social concerns and exacerbated older ones.

The first edition of this article was written in 2001. The major development since then has been the growth of 'genomics.' Impressive advances in testing, sequencing, and manipulating DNA mean we can do much more with and to DNA – faster, cheaper, and more accurately – than imagined 13 years ago. Various methods of testing first hundreds, and ultimately millions, of 'single nucleotide markers' in a human genome using 'SNP chips' now cost less than $100, leading to their widespread use in the last 15 years in scientific 'genome-wide association studies' (GWAS) as well as in consumer genomics companies. GWAS still test under a thousandth of the whole human genome, but the first reasonably complete human genome sequence was finished in 2003. It cost about $500 million (depending on the accounting conventions used). In 2014, high-quality whole human genome sequences are routinely available for about $3000 with several firms recently announcing their '$1000 genomes.' These new large-scale capabilities have shifted the focus of scientific interest from individual genes to whole or partial genomes; the scientific language has similarly been moving from 'genetics' to 'genomics,' as will, largely, this article.

At the same time, the major 'nondevelopment' has been the creeping pace of our ability to understand the effects of different DNA sequences. A major question of the last decade has been the mystery of the 'missing heritability' – researchers know, for example, that about 90% of a person's adult height comes from his combination of his parents' genes, but thus far only 10–20 percentage points of that heritability has been attributed to specific DNA sequences. As a result, the consequences of the unexpectedly enhanced sequencing capabilities of genomics have been smaller than we would have imagined.

Concern about implications of the new genetics for human societies grew with scientists' ability to decipher and manipulate DNA. The late 1960s saw discussions of human cloning, followed in the 1970s and early 1980s by safety concerns about recombinant DNA and social concerns about genetic discrimination. When the Human Genome Project was proposed for substantial funding in the United States in the late 1980s, the Project's first director, Dr James Watson, suggested that 5% of the funding be set aside to study the 'ethical, social, and legal implications' (ELSI) of human genetics (Cook-Deegan, 1994). The subsequent financial commitment led to the rapid expansion of 'ELSI' studies across many disciplines and the publication of a vast number of articles and books on these topics. The technical advances brought by genomics have accelerated the timing of some ethical, social, and legal issues, but, because of the slow pace of understanding, neither broadly nor dramatically.

Three general caveats are useful in surveying the resulting discussions of either the 'new' genetics or the 'new' genomics. First, although these new technologies often provide great power, for prediction, or for intervention, they seem unlikely to provide the extent of power often assumed in the writings about their implications. Oftentimes, their predictions will be weak; the percentage of people with a particular set of genetic variations (or 'genotype') who develop a particular trait of condition (or 'phenotype'), a percentage known as 'penetrance,' will often be low. Second, although the technologies are quite novel, their implications almost always have parallels in the social effects of other modern technologies. And third, although much of the discussion of the consequences of genomic technologies has focused on individuals or families, these technologies usually also have implications for broader human groupings. With those caveats in mind, this article will discuss the ethical, social, and legal effects of the new genomics in seven areas: health care, establishing identity, predicting the future, revealing the past, genetic manipulation, ownership and control of genetic material and information, and cultural understandings.

Issues Arising from Medical Successes

Writing on social issues of genomics focuses on the dangers of human genomics misused – lost privacy, genetic discrimination, state-enforced eugenics. It rarely looks at the potential implications of the hoped for uses of genomics to prevent and

treat diseases. The vast sums, both private and public, being spent on research in genomics are not being committed from an altruistic search for knowledge, but in the expectation that the research will bring immense medical benefits. The diseases in question may not be limited to 'genetic diseases'; genomic tools are allowing unprecedented understanding, at the molecular level, of the proper and diseased functioning of human cells and of human pathogens. The most powerful lesson of the first 40 years of the biotechnology industry has been that the human body and its functions are more complicated than expected, but those complications are steadily being tackled with genomic tools. A stream of new treatments, derived from increased knowledge of genomes and their associated proteins, is flowing through research, development, and regulatory approval, not as quickly as one would like, but persistently.

What will happen if these drugs succeed? It is possible that the results might include, among other things, a significant extension of average human life span; an increase in pharmaceutical costs; and changes, up and down, in the demand for various medical services. The social implications could be substantial, on everything from pension plans and political voting blocks to health care systems. Some more focused medical consequences of genomics research, such as individualizing patient therapies as a result of genomic tests (known as 'pharmacogenomics'), or some kinds of proposed genome therapy or tissue replacement will require that treatments be created just for one patient, thus straining the existing mechanisms for drug development, manufacturing, approval, and financing. And any new treatment will raise questions of availability, both within any one country and between countries. Genomics has created a uniquely high expectation of medical progress, which it has used to acquire funding, both public and private. If it comes close to the successes it has promised, these consequences may be raised in dramatic form.

Establishing Identity

Genomics raises four main issues centering around identity: forensic identification, personal identity, family identity, and ethnic identity.

Forensic Identification

By the mid-1990s, the new genetics was leading to major changes in forensic identification. Any tissue from a person that contains DNA can be tested for a pattern of identifying markers, sections of the genome that vary substantially from one person to another. Those markers can be compared with the markers analyzed from human tissue found in connection with a crime (National Research Council, 1992). New and powerful techniques for analyzing DNA mean that samples with only tiny amounts of genetic material can be useful, whether derived from flesh, blood, semen, or even the cells found in saliva. A negative test is very powerful. If the markers are significantly different, the tissues cannot be from the same person (unless the sample was swapped or contaminated or in a very rare case where a single person because of embryonic merger, has some tissues with one genome and some with the genome of a never-born twin). Initially, there was concern that a positive match might not be very compelling because patterns of markers might be relatively common among particular ethnic populations. That could make the odds that a match was a coincidence vanishingly small among the general population but relatively high among people from that particular ethnic group. These fears were largely assuaged through both more information on the distribution of the markers used in forensics and different techniques (National Research Council, 1996).

This forensic use of DNA is not essentially different from the use of fingerprints, blood groups, or dental records. Like those techniques, it has had to prove its effectiveness in a host of judicial cases. And, like the earlier techniques, the DNA itself can never be conclusive. Good defense counsel will always investigate the possibilities of an innocent explanation for the presence of the DNA or for mistakes, contamination, or fraud in the DNA collection and analysis process. Juries and judges might pay more attention to DNA evidence because of the high status and reputation of the science, but that effect should also fade with greater familiarity (and good defense counsel).

The real issues about the forensic use of DNA now concern not the individual case, but the collection and retention of DNA or DNA records for identification purposes. One issue concerns surreptitious collection by the police of DNA from suspects, either through an interaction with them, such as offering them something to drink and getting their DNA from the discarded container, or merely by collecting DNA from items they have had contact with, from cigarette butts to eating utensils. More broadly, many countries or states have created DNA repositories with DNA samples taken from convicted, or even merely accused, criminals. These samples can be used to seek matches in criminal cases or for the identification of human remains. If markers from the samples are analyzed in advance, the results can be put into a database and used to seek 'cold matches' to samples or tissue of unknown origin. These repositories raise two different issues. The first involves their creation. Should samples be accepted only from those who consent or should they be mandatory? If mandatory, what classes of people should be required to provide samples – convicted sex offenders, convicted felons, all those arrested, or the whole population? Litigation on this issue has become increasingly common in the United States, where all states have some form of mandatory DNA repository (*Maryland v. King*). A subtler, but equally important, issue concerns *what* the repository should contain: information on what, and how many, genetic markers? And should the DNA samples from which the profiles were derived be retained or destroyed? The markers currently used for forensic identification, as far as scientists can tell, are not strongly associated with any traits (other than sex) (Kaye and Greely, 2013). If the markers are kept, no information about a person other than identity (and possibly ancestry) can be deduced – nothing about genetically influenced disease susceptibility or other traits. (Using new markers as is currently under serious consideration, could change that.) If samples of whole DNA are kept, however, they can be reanalyzed to confirm that the profile is accurate, which may be important in some contexts, such as some international sharing arrangements. But the samples could also be analyzed for DNA associated with a wide variety of traits. This raises

much broader implications for privacy than a regime where the samples are destroyed after analysis.

Personal Identity

The furor about the possible use of somatic cell nuclear transfer (SCNT) technology to clone not just a sheep, but a human, involves a host of issues (National Bioethics Advisory Commission, 1997). Most of those issues have already been raised as a result of *in vitro* fertilization and other forms of advanced reproductive technologies. The issue unique to cloning is, in essence, a concern about human identity. Would a person with the same genome as another living individual be, in some meaningful sense, a copy of that person?

This and other speculative questions about clones were widely discussed in the aftermath of the announcement in 1997 of the birth of the cloned sheep, Dolly. Concern died down as scientists were consistently unable to produce viable human embryos using SCNT, in spite of fraudulent claims in 2005 by Dr Hwang Woo-suk. In 2013 and 2014, however, new methods did successfully produce apparently viable human embryos and embryonic stem cells from those cloned human embryos. Concern about the birth of human clones has, to some extent, revived.

Monozygotic twins, who account for about 1 in 240 live births around the world, have always shared the same genome. Although their physical similarity is strong, the individual identities, and separate personalities, of monozygotic twins have long been recognized. Cloning by SCNT, if possible in humans, could not produce individuals *more* alike than monozygotic twins. Indeed, the clone and the source of the clone's DNA would most likely be much less alike. They would have spent their first 9 months of development in the wombs of different women, subject to different environmental influences *in utero*. Once born, they would be subjected to different environments, often in very different times. The exact degree to which identical human genotypes produce similar phenotypes would be an interesting research question, in the unlikely event that it could ethically be studied. It seems quite likely that the popular perception of identity would prove grossly exaggerated.

Family Identity

Because genetic variations are inherited, parents and children share half of their genomic variations, as do siblings. Grandparents and grandchildren, as well as first cousins, share, on average, one-fourth of their genomic variations. This fact, along with cheap genomic analysis, makes it possible to use DNA to establish, or refute, close family relationships. This kind of family analysis, using inexpensive SNP chips as well as analysis of variations on the Y chromosome (found only in men and inherited directly from father to son) or the mitochondrial DNA (found in both men and women but inherited only from the mother), has led to the growth of a consumer genetic genealogy industry. At least three major firms each had hundreds of thousands of customers pay to get information about their genetic variations and to look for previously unknown genetic family members. At a more immediate level, genomic analysis can be used to try to find unknown parents, either when a mother (or a government) is trying to identify a genetic father for child support or when a child who was adopted or the product of an egg or sperm donor goes looking for genetic parents. With large enough genomic databases, close family relationships can be picked out easily. Similarly, the police can use genomic analysis to try to determine whether the source of crime scene DNA came from a close genetic relative of someone in a forensic database (Greely et al., 2006). This will become easier if the forensic databases adopt more markers, particularly on the paternally inherited Y chromosome. The ethical implications of using DNA to establish, or to refute, family relationships will vary, depending often on the consent of the family members being found or 'lost.'

Ethnic Identity

Culturally defined human groups – ethnicities or nations – often share more than common cultures, but also share a substantial degree of common ancestry. This genealogical connection implies a genetic connection; particular variations in DNA sequences, or patterns of those variations, will be more common in some populations than in others. This may apply to both common and rare variations. For example, the four ABO blood groups are genetically determined. Each one is found in all (or almost all) of the world's populations, but in different proportions. Other variations in DNA sequence may be found at elevated levels among particular groups and extremely rarely among others (Cavalli-Sforza et al., 1994).

This kind of variation can be used for anthropological research; it could also be used in an effort to define a person's ethnic identity. The latter use would have limited scientific validity; no known DNA variations are found in all members of an ethnic group and in no nonmembers of that group and given the human history of enthusiastic sexual intermixing (and of adoption or conversion), no such variations are likely to be found. Nonetheless, the rise of inexpensive genome-wide testing has led 'biogeographical' tests of an individual's ancestry becoming an important feature of popular genetic genealogy products sold to consumers, who learn that they are, for example, 87% European in origin, 11% Middle Eastern, and 2% sub-Saharan African. There have been reports of governments or ethnic groups using this kind of information for some legal purposes. The ethical implications of the naïve use of such inherently inaccurate methods for defining ethnicity are likely to depend on the circumstances, including the uses made of such definitions and whether they were adopted by the group itself or imposed on it. Any such use, however, would likely have the negative effect of reinforcing the false concept that race and ethnicity have some strong 'genetic' meaning.

Predicting the Future

The most discussed issues arising from the new genetics come from its perceived ability to make predictions about individuals' futures as a result of associations between genetic variations and physical and behavioral traits. These predictions in themselves can have implications for living people; the attempt to make such predictions prenatally can have implications for what people are born. The strength of the predictions will vary

dramatically. Some conditions, such as Huntington's disease, appear to follow inevitably from possession of a particular genetic variation. For other conditions or traits, a person with a particular genetic variation may have a somewhat increased but still small likelihood of having that condition or trait. The ethical significance of such predictions will vary largely based on who uses which predictions for what ends.

Prenatal Selection to Avoid Disease

The new genetics brought the ability to test directly the DNA of the parents and of the embryos and fetuses they conceive; genomics has made such testing increasingly practical. Where the analyzed genotypes are strongly or completely associated with particular phenotypes, whether the children might (when the parents are tested) or would (when the embryos or fetuses were tested) show those traits can often be confidently predicted. This kind of prenatal testing has been used for several decades now in efforts to avoid serious genetic diseases. Early efforts included testing for as sickle cell anemia and for Tay-Sachs disease. In some cases, prospective parents have been tested, in order to alert to them to whether such a disease is a possibility for their children. The prospective parents could use that information to avoid marriage, to avoid having children, or to seek prenatal testing during any pregnancy. This carrier testing, at least when consented to by informed patients, has been relatively uncontroversial; it is now becoming increasingly common, and broad, as commercial firms offer carrier testing for over a hundred genetic disease traits for only a few hundred dollars.

Testing of fetuses is possible only with DNA from the fetus. In the past that DNA was retrieved from cells taken from the amniotic fluid about 16 weeks into the pregnancy through amniocentesis or from the chorionic villi, part of the placenta, at about 10–12 weeks of pregnancy. Both procedures are expensive and increase the risk of a miscarriage. Since late 2011, another method has been available, the so-called 'noninvasive prenatal testing' (NIPT). This makes use of small, broken bits of the fetus's DNA that can be found in the pregnant woman's blood (along with more small bits of her own DNA). It requires only a small blood draw from the pregnant woman and can be done at least as early as the 10th week of pregnancy. By 2014, at least four U.S. companies offered this test for various chromosomal abnormalities, notably trisomy 21, which causes Down syndrome. This test also easily reveals the fetus's sex. It seems likely that, eventually, this relatively inexpensive procedure will be useful to test the fetus for any genomic variation of interest; it has already been used, in a proof of principle experiment, to recreate the fetus's entire genome sequence. Currently only a few percent of pregnancies receive genetic testing; NIPT seems likely to increase that percentage enormously (Greely, 2011).

Whatever the method, after a direct genetic test of the fetus, parents could choose to abort or could prepare themselves better for the birth of a child with the particular genetic condition. Testing of fetuses for genetic conditions has been controversial. Some have opposed it because it often leads to abortion, which they condemn as murder. Some advocates for people with disabilities have been concerned about this kind of testing, especially when followed by abortion, because they believe it implies that the lives of people with those genetic conditions are not worth living. In the United States abortion, at least until the fetus is viable outside the womb, is legal for any reason, so there has been little discussion of outlawing abortion for late onset, low penetrance, or mild genetic conditions; many countries do regulate the reasons for abortion and so face this issue. Even in the United States, a question remains as to whether governments, health care systems, and health care professionals should encourage, discourage, or be neutral on prenatal genetic testing.

A different method may change some of the discussions about prenatal genetic testing. 'Preimplantation genetic diagnosis' makes it possible to test a very young embryo before it is implanted. This procedure can only be done as part of *in vitro* fertilization because the clinicians need to have access to the early stage embryo. One cell is detached from an embryo and the DNA in that cell tested. Based on the results, the parents can decide whether to implant that embryo, or, more realistically, which of several tested embryos to implant. No fetus would be aborted; instead, some embryos would just not be implanted. In the past this procedure has been uncommon; less than 0.1% of annual births in the U.S. follow from it. That percentage may increase. New methods of genomic analysis now mean that rather than testing the embryos for one or two genetic conditions, their whole genomes could be sequenced. Furthermore, within the next few decades the need for egg harvest, the most expensive, unpleasant, and risky aspect of *in vitro* fertilization, may be avoided by using skin or other cells from a woman to make new eggs.

Prenatal Selection for Genetic 'Enhancement'

By eliminating the need to abort in order to choose genetic traits, preimplantation genetic diagnosis also increases the possibility of parents selecting children based on genetic traits that would, the parents believe, 'enhance' their children. The idea of using genetic testing to select 'enhanced' genetic traits for offspring has raised many concerns (Parens, 1998). Some fear that allowing parents to choose, or to believe they can choose, the traits of their children would deny those children their right to 'an open future' not of their parents' choosing. Others worry that the rich will be able to buy genetic advantages for their offspring, denied to those who conceive in the traditional manner. Still others worry that parental selection will lead to a homogenization of the human gene pool, as all parents opt for children with similar traits. On the other hand, some fear that some parents will want to 'enhance' their children by selecting genetic variations that most people would view as *disabilities*. For example, deaf parents might want a deaf child. Finally, some fear that these parental choices could lead to a self-perpetuating genetic caste system. Most of these results require both that genetic variations be identified that strongly predict 'success' and that many parents must be willing to undergo preimplantation genetic diagnosis. Neither is certain.

One might also question whether parents choosing to guide the choices or to enhance the chances of their children through genetics is fundamentally different from parental efforts to do the same through the environment. Rich parents send their children to 'better' schools. Parents with particular interests may push their children from an early age to excel in those

activities – Wolfgang Mozart and Tiger Woods are both successful examples. Arguably, a major goal of parenting is to 'deny' one's children certain unhappy or illegal futures. The argument that enhancement through genotype selection is inherently different or more threatening from other kinds of enhancement is not an obvious one.

Sex selection is a special case of 'genetic enhancement,' though one that can be done through sonography as well as genetic testing. In some countries, prenatal sex selection by abortion is common with female fetuses being aborted much more frequently than males. This seems likely to produce striking imbalances in the sex ratio in those countries, which may have broad social consequences. It also, some argue, reinforces the subordinate position of women in those cultures. Easier genetic testing, through NIPT or greater use of preimplantation genetic diagnosis could increase the use of sex selection (Hvistendahl).

State-Sponsored Prenatal Genetic Selection

The discussion thus far has focused on parental choices about their children's genetic makeup, but parents need not make those decisions. Governments have intervened to prevent people with 'inferior' genes from having children; such eugenics laws could come again in more precise forms. 'Eugenics' is discussed in detail in other articles and will not be reviewed here except to note two things. First, state-sponsored eugenics measures do not have to be compulsory; state actions to encourage prenatal genetic selection can also be, in a sense, eugenics. Second, the ethics of government-sponsored eugenics depends on striking a balance between government public health powers and individual procreative liberty that remains in debate.

Postnatal Genetic Testing

The possibilities of genetic testing do not end at birth. Genetic tests can help diagnose diseases or predict future disease risks. Like all medical interventions, their value depends on them being used appropriately (President's Commission, 1983; Institute of Medicine, 1993). Postnatal genetic tests provide information that can lead to a medically useful intervention, that can help the patient make life plans, and that might just satisfy a patient's desire to know her future. Genetic testing also has costs. Test results may pose psychological problems for those tested or affect the patient's relationships with family members. They may have implications for the patient's dealings with the broader society, through employment or insurance discrimination. Where tests, genetic, or otherwise, do not have powerful implications for medical intervention, the strong influence of the individual's personality and circumstances on the value of testing argues a for particularly good process of informed consent, especially when the patient's understanding of the links between genetic variations and disease may be weak. Testing children is particularly ethically suspect unless there are useful medical interventions that need to be done during childhood. Otherwise, the benefits of testing for children could be put off until they reached adulthood and were able to make their own informed decision on testing. On the other hand, when there are good early interventions, testing for children becomes more important. Most jurisdictions require, or strongly encourage, neonatal genetic testing for diseases, such as phenylketonuria, where early diagnosis can lead to interventions with enormous benefits.

Improvements in DNA analysis offer the realistic possibility of whole genome sequencing as an affordable method of genetic testing, for diagnosis or for screening. Instead of looking for just one, or a handful, of genetic conditions, whole genome sequencing offers the possibility of seeing all genomic variations. Many issues remain concerning both the analytic validity of evolving whole genome sequencing techniques – how accurately they actually analyze the DNA sequence – and, even more, the clinical validity of interpretation of whole genome sequencing – how accurately medical conclusions can be drawn from them. Other problems concern what findings to return to patients, particularly, if those problems were not the reason for the test. And determining how to provide patients with meaningful information on hundreds or thousands of genomic risks (or advantages) will prove challenging (Ormond et al., 2010). All of these issues will be particularly troubling with respect to tests of children, especially if the currently mandatory neonatal genetic testing is replaced with whole genome sequencing.

Of course, many medical tests predict higher or lower disease risks. The diagnosis of a disease, whether through genetic or nongenetic methods, can trigger many of the same costs as prediction. Genetic diseases do implicate family members to an unusual extent, but shared environments or diets can also put family members at shared risk.

Genetic Discrimination

Great concern has been expressed about the possible uses of genetic tests to discriminate against people based on genetically predicted susceptibilities. Employment, life insurance, and, in the United States, health insurance are the fields where genetic discrimination seems to be most feared. The likelihood of genetic discrimination depends on two different sets of factors: the strength of the prediction possible from genetic information and the social structure governing the relevant fields.

For someone with the allele that leads inevitably to the fatal condition, Huntington's disease, genetic prediction is quite powerful. Fortunately, such powerful genetic predictions are rare; it is not clear that employers or insurers would find significant an increased risk of diabetes from 10 to 15%. Similarly, discrimination in health insurance has been mainly a concern in the United States; all other rich countries guarantee health coverage to all, or almost all, of their residents, a direction in which the United States is moving. Even in the United States, the great majority of Americans with health insurance obtain it through methods that are not directly susceptible to genetic discrimination. Medicare, Medicaid, and employer-provided health insurance are not medically underwritten – they must accept everyone eligible without using any medical exclusions. They cover about 90% of Americans with health coverage. There is little good evidence that genetic discrimination in employment or insurance exists in the United States, although there is clear evidence of public fear of such discrimination.

Until 2008, no federal law banned genetic discrimination in insurance or in employment, although many state laws banned one or both. In 2008, the United States adopted the Genetic Information Non-Discrimination Act, known as GINA, which largely banned the use of genetic information in employment and in health insurance. GINA does not cover discrimination in life insurance, disability insurance, or long-term care insurance. The United Kingdom, where the National Health Service makes private health insurance of limited importance, has set up a regulatory authority to pass on whether or not life insurers may require tests for particular genetic conditions; the body recently approved the use in life insurance of predictive genetic testing for Huntington's disease. How well statutes limiting genetic discrimination will work remains unclear, although GINA has not yet been expensive or difficult to enforce. If some of the statutes banning genetic discrimination are able to function with relatively low costs, one might justify them on the pragmatic ground that they increase the research on and clinical use of human genetics by reducing public fears, whether or not those fears are justified (Greely, 2001).

Prediction of Behavioral Traits

The successes of the new genetics have largely been in associating genetic variations with physical traits or conditions. Much of the public interest in genetics and genomics, though, seems to lie in its possible to use to predict human behavioral traits, such as intelligence, sexual orientation, violence, or mental illness. Some human behavioral traits have been linked to genetic variations, including some forms of intellectual disability. For the most part, though, efforts to link genetic variations with human behavioral variations have, thus far, had little success and even the successes have been controversial. At this point, it is not clear to what extent genetic variations will prove able to lead to strong behavioral predictions. If such predictions were possible, the ethical implications could be substantial (Carson and Rothstein, 1999).

Strong links between genetic variations and behavior might undermine notions of personal responsibility for the involved behaviors. At the broadest level, they could affect society's view of the extent of individual free will. More narrowly, they could affect the society's view of, for example, 'genetically determined' criminal behavior or sexual orientation, although whether the result would be more or less tolerance for the behavior is not clear. These kinds of genetic predictions could also lead to interventions in individual's lives – people predicted to be likely to act violently might be put into custody before they committed any offense. The successful association of behaviors perceived as important with genetic variations would boost the interest of both parents and governments in prenatal genetic selection.

Societies make predictions about future individual behavior in many ways, from aptitude tests to past records. Except for its prenatal uses, it is not clear that doing a genetic test to determine, for example, musical ability, would offer any advantages over doing a direct test of such ability. Genetic tests would have an advantage only when the genetic prediction is strong and the behavior is not easily observed directly. At this point, it is not clear that many strong associations between human behavior and genomic variations will be discovered; the problem of 'missing heritability' has been particularly great with behavioral traits. The real ethical issues with behavioral genetics may turn out to be preventing misuse by cultures that believe in its reality even in the face of uncertain science.

Uncovering the Past

DNA can reveal aspects of the past as well as of the present. In some cases, DNA, by providing another line of evidence, can raise in new contexts issues of the privacy of historical figures in matters such as Thomas Jefferson's relationship with his slave, Sally Hemmings, or whether Abraham Lincoln had Marfan's syndrome. Other historical uses of DNA raise broader questions.

Individual Ancestry

Genetic variations can be used in a straightforward way to establish close biological relationships. Blood groups or isoforms of particular proteins have long been able to provide such information; direct DNA testing can increase the accuracy of such determinations. The ethical implications of such paternity or maternity testing vary according to its use. If done with the full consent of all relevant parties, it seems unproblematic. If done without consent of one of the parties, it might be justified, as perhaps in establishing child support obligations, but would require some consideration. One problem arises where genetic testing done for some other reason, such as attempting a diagnosis of a disorder of possibly genetic origin in a child, reveals unsought information about parentage, such as 'false paternity,' that might be unwelcome and even dangerous. Another problem could be its use by children to find sperm or egg donors who were promised anonymity.

Group Histories

Analysis of patterns of genetic variation among different human populations can reveal how closely related two populations are. This information then becomes some evidence about human history and migrations. It is not conclusive evidence, but would join with linguistic, archaeological, anthropological, historical, and other sources to improve understanding of the human past (Cavalli-Sforza et al., 1994). The information may not always be welcome. It may contradict a population's own beliefs about its history. In some situations, that information alone might destabilize or disrupt the entire culture. It could also have modern political implications where ancestral origins, and the length of time in possession of particular territories, could affect land disputes. Whether a historical researcher has ethical obligations to avoid doing research that could provoke such consequences is unclear. Similarly unclear is whether there is an ethical obligation to seek the informed consent of the entire group to such genetic research that might have consequences for the group (Greely, 1997). Such consent has not generally been thought necessary for other historical investigations affecting contemporary peoples; some might argue that 'genetic history' is different, either because of the nature of the materials being used or the different degree of certainty perceived for such 'scientific'

evidence. Somewhat similar issues arise about the necessity of obtaining permission for genetic analysis of human remains.

Manipulating Genes

The new genetics made it possible not just to read an organism's genes but to change them. The newer genomics is greatly enhancing that ability, creating additional concerns.

Somatic Cell Gene Therapy

Somatic cell gene therapy involves the placement of a human gene into a living person's somatic cells – cells that do not produce the eggs and sperm that in turn produce the next generation. Somatic cell gene therapy would aim to cure a disease only in the patient, not in the patient's descendants. It was initially conceived as introducing a properly functioning copy of a gene into a person who had a genetic disease as a result of inheriting only improperly functioning copies. Different types of somatic cell gene therapy have since been investigated for the treatment of diseases that are not primarily caused by inherited genes, such as AIDS and most kinds of cancer. Over one thousand clinical trials of somatic cell gene therapy have taken place; very few have, thus far, shown any success, although by 2014, good results were beginning to accumulate.

The genetic aspects of somatic cell gene therapy have been largely uncontroversial. In essence, gene therapy is merely another drug delivery system, a different way to get a normal human protein to the right place in the body. Somatic cell gene therapy therefore stands in the same position as most experimental therapies. Like such therapies, it has prompted concerns that desperate patients are not truly giving informed consent and that the possible benefits of the treatment are exaggerated. Gene therapy may face the latter problem to a greater extent than most experimental treatments because of the exaggerated public view of the power of anything genetic.

Germ Line Gene Therapy

Germ line gene therapy has been much more controversial (Nelson, 2000). In its usual form, it would introduce 'normal' human genes into the eggs or sperm of parents, or into the fertilized egg or early embryo of the offspring. The goal would be to change the eventual child's genetic inheritance. This could be done in order to avoid a genetic disease or in order to introduce an 'enhancing' genetic variation. No one has tried human germ line gene therapy in its classic sense; indeed, there has been an informal moratorium in the scientific community on trying such experiments in humans. Both its feasibility and its value are unclear.

New genes have been successfully introduced into the germ lines of other mammals, but with low efficiency. At the same time preimplantation genetic diagnosis allows parents to choose embryos based on their genetic variations, as long as the parents themselves produced the desired variations. If not, donated eggs or sperm would likely be a much safer and easier way to introduce the desired genes than germ line cell gene therapy; ultimately, somatic cell gene therapy might provide another way for parents to change their offspring's genetic variations.

One kind of germ line gene therapy is plausible, has been tried, and is currently being debated: mitochondrial transfer. The mitochondria, organelles found in all eukaryotic cells, including human cells, have their own very small genome. In humans, mitochondria, and hence the mitochondrial genome, are inherited only from a child's mother. If the mother's mitochondrial genome has variations that cause disease, all of her children will carry the same pathogenic DNA. This can be avoided by combining the nucleus of an egg from the woman who wants children with mitochondria from a woman with a healthy mitochondrial genome. At least one *in vitro* fertilization clinic in the United States tried this procedure in the late 1990s and early 2000s, but abandoned it when the Food and Drug Administration asserted jurisdiction over the procedure. In 2014, researchers have sought approval from authorities in both the United Kingdom and the United States to resume experiments with this mitochondrial transfer procedure, which would allow afflicted women to have children without their disease, but would change the genomes of all cells of the children, including their egg and sperm – though only the female children could pass on their mitochondrial DNA. These efforts have been quite controversial, raising concerns about children with 'three parents.'

Chimeras

The manipulation of genes permits the creation of 'chimeras,' creatures that are genetically a mix of two species, including organisms that could not possibly mate. In agriculture, this mixing of genes from very different organisms has been perceived by many as unethical and potentially dangerous. Unless one takes a strong view of the reality and sanctity of sharp lines between species, it is hard to develop a strong ethical argument against such mixes. On the other hand, one might argue that a gene in the new setting of a different species might develop different and possibly harmful functions than in its home species.

Chimeras involving human genes could provoke greater concern. Intentionally moving nonhuman genes into humans could be seen as lessening the humanity of the recipient; moving human genes into nonhumans could be seen as investing nonhumans with some aspects of humanity. The former has not been attempted; the latter, however, is routine. Most of the products of the biotechnology industry, including insulin, erythropoietin, and human growth hormone, are made by creatures that are genetically partially human and partially nonhuman. Human genes are transferred into useful host cells such as yeast, which then produce large amounts of the human protein for which the gene codes. Of course, an organism with 5300 yeast genes and one human gene does not seem very human; to be concerned about this kind of chimera would require a very strong belief in the essentially human, or sacred, nature of any human DNA sequence. Moving more human genes or moving human genes into more closely related organisms, such as chimpanzees, could provoke more serious concern about blurring the definition of humanity.

Artificial Genes or Genomes

It is possible for scientists to create 'new' genes, not found in any existing species, that would create new or modified proteins. One branch of the biotechnology industry specializes in such efforts, named 'directed evolution.' The technology takes related genes from different species, recombines them or makes mutations in them, and then examines how well the resulting protein functions. Similarly, scientists could construct, piece by piece, a novel genome. Placed inside a cell, it might be able to generate a new living organism. One research team has already synthesized the genome of one bacterium, inserted it into a related bacterium, and the resulting organism lived, reproduced, and seemed ultimately indistinguishable from the first bacterium. In 2014, another group synthesized, with a few changes, chromosome 3 of the 16 in a common yeast, used it to replace a natural copy of chromosome 3, and produced a viable yeast cell. New methods of synthesizing DNA, coupled with new methods for targeted replacement of specific existing DNA with synthesized DNA (particularly a method called CRISPR) greatly increase the possibilities of genomic editing. These techniques are unlikely to be used soon in humans, where the safety consequences are potentially enormous, but may well be used to transform bacteria, plants, and nonhuman animals. Recreating recently extinct species may be possible; creating quite new species – from algae for biofuels to unicorns for entertainment – is also plausible.

The safety of making new genes, and hence new proteins, or new genomes, and hence new organisms, is an obvious concern. The deeper concern would be whether humanity should 'play God' by intentionally creating such new entities. Of course, since the invention of agriculture, humans have created new kinds of organisms by cross-breeding between species and by selective breeding within species. New genes are created whenever a gene is mutated, which is sometimes a conscious step in experiments with nonhuman organisms. The speculative possibilities outlined here are more significant, and less accidental, interventions. It is not clear whether that makes them ethically different.

Ownership and Control

Research

Rules governing the conduct of human genetics research control the research subject's genetic materials and information. These rules generally require the informed consent of the subject to the research. Research subjects, however, rarely have any control over the subsequent uses of materials or information derived from them (Greely, 2007). The California Supreme Court decision in *Moore v. Regents of the University of California* (1990) ruled that the plaintiff could not assert a property interest in a cell line derived from cells taken from his body, although it allowed him to try to prove that the physician–scientist had not gotten his informed consent. There have been few court decisions on this point, but current practice generally follows *Moore* and gives research subjects no control over who can use their previously collected genetic materials and information, for what purposes, or for how long. Current practices also discourage any sharing of financial benefits of the research with the subjects on the theory that the hope of such benefits could be an 'undue inducement' to them to take part in the research.

Since the late 1990s, the improved ability to analyze DNA has led a new approach to human genomics research. This associational research seeks to find weak connections between genetic variations and disease by searching for correlations between the genotypic and phenotypic data of large groups of people. Originally, it was undertaken using SNPs, increasingly it can be done with whole exome or whole genome sequence data. This kind of research requires the creation of a resource made up of health records and DNA samples (which are then analyzed for their genotypes) of hundreds of thousands of people. These resources would be too expensive to be created for the study of one kind of illness. Instead, the resources would contain complete medical information and be available to test a wide range of hypotheses. Iceland provided the first large example of this kind of 'genotype/phenotype resource' or biobank, when the government gave a private firm, deCODE Genetics, the license to create a health records database with clinical, medical, and genetic information on all 275 000 residents of the country.

For the genealogical information and health records of Icelanders, the Icelandic legislation provided that consent was presumed; unless an Icelander returned a government form 'opting out' of the database, their records would be included. Explicit consent was required for the inclusion of a person's DNA information. The Icelandic plan raised numerous ethical concerns, including the use of presumed consent, the absence of discussion of the risks and benefits of specific research done on the resource, the degree that privacy would be protected, the access (if any) of other researchers to the company's data, the propriety of having a for profit company control this information, and the financial fairness of the agreements between Iceland and deCODE (Greely, 2000). The Iceland/deCODE plan ultimately foundered, largely for financial reasons, but other countries have created similar biobanks, notably the United Kingdom with its UK Biobank made up of samples and data from 500,000 volunteers with current plans to sequence the whole genomes of at least 100,000 of the participants. These biobanks raise similar issues. Soon, however, even bigger 'virtual' biobanks are likely to exist. Once a substantial number of patients have their whole genomes sequenced for medical purposes, all of their health information and their entire genome sequence will be stored in their electronic medical records. This will be an irresistible and potentially population-wide source of data for researchers; what kinds of consent or control will be required from the patients is unclear.

Patents

No single case unequivocally announced that genes, or human genes, could be patented, but when the U.S. Supreme Court, in *Diamond v. Chakrabarty*, approved a patent on a genetically altered bacterium, it started a continuing debate over the patenting and genetics (*Diamond v. Chakrabarty*, 1980). To many patent lawyers, DNA is just another organic molecule. Patenting of forms or parts of it seems them to fall within long-established principles concerning the composition of matter patents on molecules not found in pure or refined form in

nature (Eisenberg, 1990). Others objected to some or all gene patents on a variety of grounds. Those objections can be put into two categories: fundamental and technical.

Some people have fundamental objections to patents on genes, on human genes, or on genetically modified life forms. One set of objections, focusing on genes, contends that they are 'discoveries,' not 'inventions,' and so should not be patented. Others point out that genes were made by God, nature, or evolution – in any event, something other than those filing the patent claims – and should not be allowable as intellectual property. Another objection is that human genes are the common heritage of mankind and should not be 'owned' by anyone but should be held in common. Still others oppose gene patents as part of broader opposition to biotechnology; forbid genetic patents and the technology would, at least according to the industry, be slowed. Proponents of gene patents put forward answers to each of these objections; throughout the industrialized world, the proponents won. Patents on genes, human genes, and to a somewhat lesser extent genetically modified life forms were commonly allowed in the United States, Europe, and Japan. It is worth noting, though, that most patents expire 20 years from the date of application. The first wave of gene patents has already expired; presumably all patents on human genes will have expired by 2021, 20 years from the publication of a draft of 'the human genome.'

This broad picture was upset when the United States Supreme Court ruled in *Association for Molecular Pathology v. Myriad Genetics* (*Association for Molecular Pathology v. Myriad Genetics*, 2013) that naturally occurring genomic sequences could not be patented as 'compositions of matter' because they were 'products of nature.' The Court did say that humanly modified genomic sequences, such as 'complementary DNA,' could be patented. The *Myriad* case did not deal with patents on uses of DNA, although a slightly earlier Supreme Court decision, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* (*Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 2012) has limited the power of patents on genetic tests. The Court held that a test that compared the level of a molecule in a patient's blood to a known set of ranges and made dosing decisions as a result could not be patented because it was a 'law of nature.' That doctrine has already been used to invalidate patents on the process of comparing the sequence of a patient's BRCA 1 and BRCA 2 genes with known 'safe' and 'dangerous' sequences for the purpose of assessing cancer risk. The ultimate results of these Supreme Court decisions on the patentability of genes, genomes, and genomic technologies remain unclear.

Privacy

Protecting the privacy of genetic information is one way to control its use (Annas et al., 1995; Rothstein, 1997). But such 'genetic privacy' legislation raises its own set of problems.

The first problem is definitional – what is the 'genetic information' that should be protected? Information about a person's genetic variations can come from DNA tests, from other biochemical tests, from a naked eye examination, or from family history. A narrow definition, focusing on the results of 'genetic tests,' would miss such powerful information as the 50% chance that the child or sibling of a Huntington's disease patient carries the Huntington's allele. A broad definition, covering everything from which an inference can be drawn about a person's genotype, would cover almost all medical information. A very high cholesterol level is strong evidence that a person carries two alleles for familial hypercholesteremia. An average or low level is strong evidence that he or she does not. GINA deals with this problem, but mostly in the context of forbidding the use of genetic information to discriminate against people in employment or health insurance; not as a general privacy protection of such information.

If almost all medical information leads to inferences about genotypes, it may not make sense to try to protect 'genetic information' separately from medical information. And it may not be possible to 'protect' a person's medical information from the many institutions that have legitimate uses for it, including physicians; hospitals; and those employers, insurers, and governments that pay health care bills. At the same time, the passage of legislation expressly to protect 'genetic' information sends the public the inaccurate message that genetic information is always much more powerful and important than other medical information. Legislation to protect genetic privacy has been introduced in the United States Congress but has not been passed. Several states have passed such legislation, but it is too early to tell how effective that legislation will prove.

Cultural Consequences

The most far-reaching, but hard to predict, ethical implications of genomics may lie in its effects on society's beliefs. Three areas stand out.

First, genomics demonstrates, in a very powerful way, that all life on earth is related. Over one-third of the genes found in the single-celled brewer's yeast have recognizable relatives in the human genome. Some stretches of DNA appear in close to identical form between humans, mice, and fruit flies. Indeed, there appear to be few specifically 'human genes' but many human variants of genes shared by all mammals, vertebrates, multicellular creatures, or life forms generally. Darwin's thesis that all earthly life is related by descent from a common ancestor can be seen in these similarities in DNA. It is unclear what cultural significance, if any, this will have. It could not promote vegetarianism, because genomics shows that carrots and corn, like sheep and cattle, are our relatives. It might, however, promote greater respect for nonhuman life.

Second, the new genetics shows that all humans are closely related. Humans are all cousins. Our DNA differs, on average, at one spot in 1000. In the regions of the genome that code for protein, the differences are one base pair in 10 000. Humans from opposite ends of the earth are far more similar to each other genetically than are chimpanzees from the same band. Genetic theories were used to provide support for a 'scientific' racism in the first part of the twentieth century. Genomics should provide evidence against such racism.

Third, genetics may shift the balance in the cultural debate between nature and nurture as the source of human characteristics (Degler, 1991). Dr James Watson, codiscoverer of the structure of DNA, was famously quoted as saying "We used to think that our fate was in the stars. Now we know that our fate

lies in our genes." In a debate that has raged for centuries, DNA may appear to be proof that individuals are powerfully shaped by forces beyond their control. In fact, genomics paints a more complicated picture. Genes play a role in the development of many traits or diseases, but the environment or luck may also be essential. The general population seems to hold a much stronger belief in the power of genes. For that reason, genomics could end up promoting a more closed and fatalistic view of human life and abilities than either current society holds or science would support (Nelkin and Lindée, 1995). That reaction may prove to be the most significant ethical challenge of the new genetics.

See also: Biobanking: Ethical Issues; Bioethics in the Post-genomic Era; Bioethics: Genetics and Genomics; Direct-to-Consumer Personal Genetic Testing; Ethical, Legal, and Social Implications Program at the National Human Genome Research Institute; Eugenics as an International Movement; Eugenics, History of; Forensic Genetic Databases: Ethical and Social Dimensions; Genetic Counseling: Historical, Ethical, and Practical Aspects; Genetic Engineering; Genetic Screening for Disease; Genetics and Forensics; Genetics and Social Justice; Genetics and Society; Genetics, Disease, and Reproduction; Genetics: Legal Aspects; Genetics: The New Genetics; New Genetics and Race; Race: Genetic Aspects.

Bibliography

Annas, G.J., Glantz, L.H., Roche, P.A., 1995. The Genetic Privacy Act and Commentary. Boston University School of Health, Boston, MA.

Association for Molecular Pharmacology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2013.

Bobinski, J.A., 2000. Genetic information, legal, ERISA preemption, and HIPAA protection. In: Murray, T.H., Mehlman, M.J. (Eds.), Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology. John Wiley & Sons, New York.

Carson, R.A., Rothstein, M.A. (Eds.), 1999. Behavioral Genetics: The Clash of Culture and Biology. Johns Hopkins Univ. Press, Baltimore, MD.

Cavalli-Sforza, L.L., Menozzi, P., Piazza, A., 1994. The History and Geography of Human Genes. Princeton Univ. Press, Princeton, NJ.

Cook-Deegan, R.M., 1994. The Gene Wars: Science, Politics, and the Human Genome. Norton, New York.

Degler, C.N., 1991. In Search of Human Nature: The Decline and Revival of Darwinism in American Social Thought. Oxford Univ. Press, New York.

Diamond v. Chakrabarty, 444 U.S. 397, 1980.

Eisenberg, R.S., 1990. Patenting the human genome. Emory Law Journal 39, 721–745.

Greely, H.T., 1997. The control of genetic research: involving the "Groups Between". Houston Law Review 33, 1397–1430.

Greely, H.T., 2000. Iceland's plan for genomics research: facts and implications. Jurimetrics Journal 40, 153–191.

Greely, H.T., 2001. Genotype discrimination. Pennsylvania Law Review 149, 1483–1505.

Greely, H.T., Riordan, D.P., Garrison, N.A., Mountain, J.L., 2006. Family ties: the use of DNA offender databases to catch offenders' kin. Journal of Law, Medicine & Ethics 34, 248–262.

Greely, H.T., 2007. The uneasy ethical and legal underpinnings of large-scale genomic biobanks. Annual Review of Genomics and Human Genetics 8, 343–364.

Greely, H.T., 2011. Get ready for the flood of fetal gene screening. Nature 469, 289–291.

Hvistendahl, M., 2011. Unnatural Selection: Choosing Boys over Girls, and the Consequences of a World Full of Men. Public Affairs, New York.

Institute of Medicine, U.S. National Academy of Sciences, 1993. Assessing Genetic Risks: Implications for Health and Social Policy. National Academy Press, Washington, DC.

Kaye, D.H., Greely, H.T., 2013. Brief of genetics, genomics and forensic science researchers as Amici Curiae in support of neither party. Jurimetrics 54, 43–64.

Maryland v. King, 133 S.Ct. 1958, 2013.

Mayo Collaborative Services V. Prometheus Laboratories, Inc., 132 S. Ct. 1289, 2012.

Moore v. Regents of the University of California, 51 Cal.3d 120, 1990.

National Bioethics Advisory Commission, 1997. Cloning Human Beings. NBAC, Rockville, MD.

National Research Council, 1992. DNA Technology in Forensic Science. National Academy Press, Washington, DC.

National Research Council, 1996. DNA Technology in Forensic Science: An Update. National Academy Press, Washington, DC.

Nelkin, D., Lindée, M.S., 1995. The DNA Mystique: The Gene as a Cultural Icon. W.H. Freeman, New York.

Nelson, R., 2000. Gene therapy, ethics, germ cell gene transfer. In: Murray, T.H., Mehlman, M.J. (Eds.), Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology. John Wiley & Sons, New York.

Ormond, K.E., Wheeler, M.T., Hudgins, L., Klein, T.E., Butte, A.J., Altman, R.B., Ashley, E.A., Greely, H.T., 2010. Challenges in the clinical application of whole-genome sequencing. The Lancet 375, 1749–1751.

Parens, E., 1998. Enhancing Human Traits: Ethical and Social Implications. Georgetown Univ. Press, Washington, DC.

President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research, 1983. Screening and Counseling for Genetic Conditions: A Report on the Ethical, Social, and Legal Implications of Genetic Screening, Counseling and Education Programs. The Commission, Washington, DC.

Rothstein, M.A. (Ed.), 1997. Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era. Yale Univ. Press, New Haven, CT.