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THE GHOST IN OUR GENES: LEGAL AND ETHICAL IMPLICATIONS OF EPIGENETICS

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Abstract

Epigenetics is one of the most scientifically important, and legally and ethically significant, cutting-edge subjects of scientific discovery. Epigenetics link environmental and genetic influences on the traits and characteristics of an individual, and new discoveries reveal that a large range of environmental, dietary, behavioral, and medical experiences can significantly affect the future development and health of an individual and their offspring. This article describes and analyzes the ethical and legal implications of these new scientific findings.

> *"At the heart of this new field [of epigenetics] is a simple but contentious idea — that genes have a 'memory.' That the lives of your grandparents — the air they breathed, the food they ate, even the things they saw — can directly affect you, decades later, despite your never experiencing these things yourself." BBC, Ghost in Your Genes.*

I. INTRODUCTION

Following completion of the sequencing of the human genome in 2003, the functional analysis of the human genetic code seemed to be a relatively straightforward task. In fact, notwithstanding the enormous progress in understanding the genetic basis of diseases and other traits made possible by the Human Genome Project, full understanding of human genetic processes has turned out to be far more complex than initially expected. Perhaps the most important of these complexities is epigenetics, which plays a major role in the expression of human genetic traits. From cancer to environmental toxicity to maternal behavioral effects to *in vitro* fertilization risks, epigenetic effects play an important, previously under-appreciated role in the interaction of nature and nurture to determine human traits.

Epigenetic changes are alterations in the chemical modification of DNA that do not involve modifying the actual DNA sequence, which is the genetic information coding for the various inherited traits and predispositions in humans and other organisms. Although epigenetic effects do not change the genetic code per se, they leave "marks" on the DNA sequence, which in turn affect whether, when, and how specific segments of the genetic code are turned on or "expressed." Accordingly, the genetic code has been compared to the hardware of a computer, whereas epigenetic information has been compared to computer software that controls the operation of the hardware.[1] Further, the factors that affect the epigenetic information may be analogized as parameters for operating the software.

There is growing awareness of the importance of epigenetics from both a health and policy perspective.[2] This is due in large part to the realization that the epigenome is highly sensitive and responsive to environmental influences, including toxic exposures, dietary factors, and behavioral impacts. While the nature and importance of at least some epigenetic changes are well-established, many of the implications and mechanisms of epigenetics remain uncertain or speculative. Although the term epigenetics has been used for decades, most of the progress and insights in understanding epigenetics has occurred in the past decade, and much remains to be understood. Several major scientific undertakings have recently focused efforts on epigenetic research, and significant new developments in this field are occurring on a continual basis. It is clear that epigenetics is an enormously important and generally under-appreciated mediator between the environment and genetics, and epigenetics is already presenting important regulatory, legal, and ethical issues.

This article provides an initial exploration of the legal and ethical implications of the rapidly emerging science of epigenetics. Part II defines epigenetics, summarizes the characteristics of epigenetic mechanisms, and describes the current state of research in this emerging field. Some examples of effects that can result from aberrations in epigenetics are also discussed. Part III explores legal issues raised by epigenetic data, including both regulatory and litigation applications. Part IV addresses the ethical implications of epigenetics. Part V concludes by noting the conceptual and practical challenges in societal responses to epigenetics.

II. BACKGROUND

A. Description of Epigenetics

The term "epigenetics" was first introduced in 1942 by Conrad Waddington to describe the interactions of genes with their environment, which bring the phenotype into being.[3] Today, epigenetics refers to modifications of the genome that do not involve a change of DNA sequence (i.e., the A's, C's, G's and T's that code information in DNA).[4] Until recently, most genetic variation was believed to be caused by mutations that change the DNA sequence, thus resulting in altered gene products with different properties affecting the development of phenotypic traits, such as eye color, metabolism, and disease susceptibility.[5] While epigenetic changes can result in changes in the expression of these same traits, they do so not by changing the form or function of gene products, but by altering the timing and quantity of their

production in tissues at key points in time.[6] Changes in determining which genes are expressed and their degree of expression can have dramatic effects on the development and characteristics of an organism.

Some epigenetic changes involve chemical alterations to the DNA molecule itself, most commonly the addition of a methyl group to cytosine bases (the "C's") to form methyl-cytosine,[7] which makes the DNA molecule in that region less likely to be expressed. This binding predominantly occurs at sites where a C precedes a guanine ("G") base to form what is referred to as a CpG site.[8] In somatic cells, approximately 70 percent of the over 28 million CpG units in the human genome are normally methylated, helping to suppress expression of many genes.[9] CpG sites often are clustered upstream of many mammalian genes to form CpG islands. These upstream regions are often the "promoter" region of a gene, where the binding of a specific molecule (the "promoter protein") that recognizes the promoter sequence will cause the gene to be expressed.

When the CpG islands are relatively unmethylated, that region of the chromosome is in an "open" configuration that permits increased accessibility to the gene promoter.[10] In contrast, binding of a methyl group to a cytosine base makes the DNA strand less available to be expressed. If enough of the cytosine bases in a CpG island upstream of a gene are methylated ("hypermethylation"), these epigenetic changes will turn off the gene. There is thus an inverse relationship between DNA methylation and gene expression.[11] Methylation is responsible for the normal suppression of many genes in somatic cells.[12]

Other epigenetic changes involve chemical alterations to the proteins that bind with DNA to form chromosomes, including methylation or acetylation of histone proteins that bind with DNA and affect the higher-order structure of chromosomes and the nucleus.[13] For example, the acetylation of histone proteins signals an open configuration of the chromosomal region that promotes expression, whereas deacetylation causes the chromosome to become more compacted and inactive.[14] The third and most recently discovered type of epigenetic effect is RNA interference, which involves RNA molecules produced from DNA binding back to the DNA at specific sites to turn off gene expression.[15] Although the various types of epigenetic changes have generally been studied separately until recently, "[i]t is becoming clear that significant crosstalk exists between different epigenetic pathways."[16] Each epigenetic change is referred to as a "mark," and the total set of epigenetic marks in an organism is referred to as the epigenome.

An important aspect of epigenetic changes is that they are durable, have a propensity to spread, and can even be transmitted from one generation to the next. Some epigenetic alterations, in particular DNA methylation changes, are inheritable both from a progenitor cell to its progeny cells through the process of mitosis (cell division), and from a progenitor organism to its progeny organisms through the process of meiosis (sexual reproduction).[17] Thus, for example, when the DNA strand copies itself when a cell divides, the methyl groups on the parent DNA strand are copied onto the new daughter DNA strand. A growing body of evidence exists in animals, plants, and humans that epigenetic effects induced by many types of stimuli and interventions–including nutrition, endocrine disrupting chemicals, maternal care, and maternal stress–can be inherited transgenerationally and affect subsequent generations.[18]

Another important aspect of epigenetic effects is that they are sensitive to the stage of development, at which epigenetic patterns are subject to reconfiguration or "reprogramming."[19] The age at which an organism is exposed to epigenetic-altering substances or behaviors is therefore a critical factor affecting the consequences of such exposure. Exposures to developing fetuses at the gestation stage and newborn offspring involve the most sensitive periods for many epigenetic effects.[20]

B. The Roles of Epigenetic Programming in Normal Cells

Epigenetics plays several important roles in normal cells. The primary function of epigenetic programming is to control cell differentiation through differential gene expression.[21] Every somatic (i.e., non-gametic) cell in the human body has essentially the same genetic material.[22] Yet, different cell types, whether skin cells, muscle cells, bone cells, or nerve cells, display markedly different properties due to different sets of genes being turned on or off. Because different cell types maintain their fate during cell division even though their DNA sequences remain the same, essentially, the developmental processes are regulated largely by epigenetic mechanisms that turn off unneeded genes in a tissue-specific pattern.[23]

A second function of epigenetic programming is to control transposable elements in the genome. Transposable elements or transposons, sometimes referred to in the vernacular as "jumping genes," are DNA segments that have the capability and propensity to jump around the genome. These sequences are very common in the human genome (estimated to comprise up to 50 percent of the entire human genome),[24] they tend to be highly repetitive sequences, and they probably originated from viruses or other pathogens and subsequently became integrated into the human genome.[25] While some movement of transposable elements around the genome can generate new genetic variation and flexibility, such movement can be damaging by integrating and disrupting other important genes, potentially resulting in mutation and cancer-generating changes. Epigenetic programming often silences these disruptive sequences by making the surrounding chromatin more compact, thereby inhibiting the replication and transposition of transposable elements.[26]

A third epigenetic function in normal cells is a process known as "imprinting."[27] Usually, both copies of a gene in the human genome are expressed, but some genes are subject to imprinting, which selectively "turns off" either the copy of the gene received from the mother or the copy received from the father. Several hundred human genes, or approximately one percent of human genes, are believed to be subject to this imprinting phenomenon, which involves DNA methylation.[28] The leading theory for explaining gene imprinting is that it represents a battle between the sexes, known as the parental conflict hypothesis.[29] According to this hypothesis, genes that cause a mother to devote more energy and resources to its developing offspring tend to favor the reproductive success of the father's genes (in the form of the embryo) over the mother's well-being, and for such genes the paternal version tends to be expressed while the maternal version is silenced in the offspring.[30] Conversely, genes that do not sacrifice the mother's health for the benefit of the offspring tend to be maternally expressed with the paternal contribution silenced. One implication of this "battle of the sexes" played out through epigenetic imprinting is that it matters from which parent you get a gene. It may also explain why some conditions, including autism, Alzheimer's disease, bipolar disorder, and schizophrenia, have higher risks of being passed on to the next generation depending on whether the mother or father has the condition.[31] In ad-

dition to genes imprinted in a parent-of-origin-specific manner,[32] other genes seem to be randomly imprinted, with up to five percent of human genes having only one or the other copy expressed in a given tissue, resulting in yet another epigenetic mechanism producing divergent genetic expression from the same genotype.[33]

Finally, and perhaps most significantly from the perspective of public policy and health protection, epigenetics provides a mechanism for a developing organism, either in utero or postnatally, to assess its environment and adjust its genetic response accordingly. The powerful influence that epigenetic effects can have on the expression of genes, and thus the organism's resulting phenotype, provides a rapid feedback mechanism by which an individual's environment can influence its genetically-programmed development. Such mechanisms allow a developing organism to adjust its phenotype to its anticipated environment, thereby increasing its fitness (provided that the environment does not change significantly between the organism's early developmental stages when epigenetic patterns are set and the adult environment).[34] Various factors, such as diet, lifestyle, and environmental exposures, can affect the epigenetic status of human and other organisms, helping to direct their development.[35]

As discussed above, the individual is particularly sensitive to these epigenetic influences at certain early stages of development. As one writer succinctly described this dynamic, "[t]he notion is that we experience periods in development when our bodies are programmed to collect information about our environment, then readjust our growth depending on what we find."[36] This flexibility allows an individual organism to adapt its genetic expression to the environmental conditions it encounters in early development, without the necessity of permanent changes to the genome that would limit the flexibility of future generations that may experience very different conditions.[37] As succinctly summarized by one leading epigenetics researcher, epigenetics allows an organism to rapidly "respond to the environment without having to change its hardware."[38]

By this mechanism, environmental factors produce changes in gene expression and resulting genetic characteristics over an individual's lifetime, rekindling the early nineteenth century concept of the heritability of "acquired characteristics" attributed to Jean-Baptiste Lamarck.[39] By providing a mechanism by which environmental factors can influence the expression of genes, epigenetics acts as a mediator between the environment and the genome.[40]

As discussed further below, when certain environmental factors affect a critical epigenetic control in the rapidly developing organs, it often leads to diseases in the person exposed.[41] Some epigenetic changes leading to cancers and other diseases have been found to be transgenerational with nearly 100 percent penetrance, in that the altered epigenetic pattern can be transmitted to subsequent generations effectively without physically being exposed to the original trigger of the epigenetic change.[42]

C. Examples of Abnormal Epigenetic Effects

Although epigenetic mechanisms are important for normal development, the disruption of epigenetic processes can lead to detrimental consequences. As one recent review noted, "[j]ust as epigenetic change is at the heart of normal development, so also do disruptions in epigenetic modifications disturb

normal developmental programs."[43] Some prominent examples of epigenetic aberrations that can adversely affect human health and welfare are summarized below.

1. Cancer It is now widely accepted that epigenetics plays a key role in many cancers,[44] and indeed DNA methylation has even been referred to as the "hallmark of cancer."[45] Two types of abnormal DNA methylation patterns are observed in virtually all human cancers, including colon, breast, prostate, and lung tumors.[46] First, genome-wide hypomethylation, or the loss of methylation, has been demonstrated in almost all human tumor types.[47] This loss of methylation could result in the activation of normally suppressed oncogenes, which are genes that promote tumor formation, thereby increasing the risk of cancer.[48] The degree of hypomethylation of many tumors is related to the aggressiveness of the tumor: as the tumor becomes progressively demethylated it becomes more dangerous and invasive in form.[49] The overall reduction of methylation in cancerous cells is accompanied by increases in methylation (hypermethylation) at specific sites in the genome. Second, more localized hypermethylation of the promoter regions of tumor suppression genes that normally help the cell stave off tumor formation results in reduced expression of those genes, and hence increased risk of tumor formation.[50] In mice, experimental data directly demonstrate that this global hypomethylation and localized hypermethylation can cause cancer.[51]

Another epigenetic mechanism of cancer causation is loss of imprinting. Aberrant activation of the normally silent copy of an imprinted growth-promoting gene, or aberrant silencing of the normally expressed copy of an imprinted tumor suppressor gene, can result in cancer formation.[52] For example, in Beckwith–Wiedemann syndrome,[53] loss of imprinting of two neighboring stretches of the DNA on the maternal chromosome that are normally imprinted disrupts the normal function of the cells in responding to internal or external environmental cues.[54]

2. Adult Onset Diseases Scientists have established that DNA methylation patterns change throughout the stages of human development, and changes are the most drastic during embryogenesis. Strong evidence supports the notion that predisposition to various types of diseases that do not manifest until later in life may be encoded epigenetically at early developmental stages.[55] This theory, sometimes referred to as the "early origins" or fetal basis of adult disease model,[56] hypothesizes that "the evolution of developmental plasticity, which enables an organism to adapt to environmental signals during early life, can also increase the risk of developing chronic diseases when there is a mismatch between the perceived environment and that which is encountered in adulthood."[57] Evidence links DNA methylation to common late onset diseases, such as hypertension, diabetes, obesity, schizophrenia,[58] and bipolar disorder;[59] developmental disorders, such as Beckwith-Wiedemann syndrome, Angelman syndrome,[60] Prader-Willi syndrome;[61] and other disorders, such as Alzheimer's disease, asthma, and coronary artery disease.[62]

An intriguing example of such an effect is growing evidence from both animal and human studies that nutritional scarcity in early development epigenetically programs individuals with a "thrifty" phenotype that allows them to maximize energy and growth from scarce food resources.[63] Once established in early development, this phenotype is fixed for the lifetime of the individual. However, if the individual encounters different conditions later in life where food is more abundant, the epigenetic programming will now mismatch with the environment, with the result that the individual is prone to developing condi-

tions such as obesity and Type 2 diabetes.[64] For example, a study of 300,000 young men born before, during, and after an extreme eight-month famine in the Netherlands during World War II found a significantly higher incidence of obesity in those individuals who were in the first two trimesters of in utero development during the famine.[65]

3. Transgenerational Effects of Endocrine Disrupting Chemicals Maternal exposure to hormone disrupting chemicals (or endocrine disruptors), such as xenoestrogens, oestrogenic (estrogenic), and hormone mimicking chemicals, may interfere with the epigenetic reprogramming of the fetal germline at key stages of early development, resulting in transgenerational adverse effects. Perhaps the best-known example of such effect is from diethylstilbestrol (DES), an estrogenic pharmaceutical agent given to pregnant women from the 1940s to the early 1970s to avoid miscarriage. DES ingestion increased the risk of reproductive disorders and rare forms of cancer in DES daughters and granddaughters.[66] Animal tests suggest the effects of maternal DES exposure were transmitted through the maternal germline to offspring via both genetic and epigenetic mechanisms.[67]

Although DES has been banned for several decades, other endocrine disruptor chemicals may operate through epigenetic mechanisms to adversely affect human health. For example, vinclozolin, a fungicide used on a number of crops such as grapes and strawberries, induces a wide variety of adverse effects, including spermatogenic abnormalities, male infertility, breast cancer, and kidney disease, in animal tests, not only in the first generation but also in generations two through four.[68] These abnormalities occur at frequencies ranging from twenty to ninety percent of individual animals in subsequent generations, an enormously high rate that is consistent with an epigenetic mechanism.[69] Although exposure levels in this study were much higher than typical environmental exposures, the study is important for demonstrating that endocrine disrupting substances can have epigenetic effects that are passed on to several subsequent generations.

4. Ionizing Radiation Modern low radiation cancer therapy has led to increased patient survival rates. However, one of the radiation treatment-related complications is the potential risk of genome instability in the progeny of radiation-treated parents. At this time, there is no conclusive evidence of increased risk of genetic disease in offspring of long-term survivors of cancer.[70] In animal experiments, X-ray irradiation produced trans-generational male germline-specific epigenetic mutations, which means: an elevated mutation rate in the reproductive cells that persists in subsequent generations.[71] Therefore, low-dose radiation may directly affect methylation and chromatin structure. In humans, a significant reduction of global cytosine DNA methylation and the levels of enzymes responsible for maintaining methylation were observed in the thymus tissue of the offspring of radiation-exposed parents.[72] Given this observation of significant damage to the epigenetic regulation system in the offspring, it is possible that the resulting genome destabilization may be a precursor for transgenerational carcinogenesis.[73]

5. Smoking and Air Pollution Exposure to toxic contaminants in tobacco smoke has been found to influence the development and health of subsequent generation(s).[74] One study reported that fathers who started smoking before age eleven have sons of heavier average weight at age nine, compared to sons whose fathers smoked later in their life or never smoked.[75] The same study also showed that paternal smoking does not affect the weight of daughters, but does induce sex-specific, male germ-line transgenerational responses in the male offspring.[76] Another study found that grandchildren of grandmothers

who smoked during the fetal period had an increased risk of developing asthma in their first five years of life.[77] With respect to air pollution, a recent study found that exposure of mice to diesel exhaust particles and allergens induced methylation changes beyond what occurred with exposure only to the allergen, suggesting that such changes may be involved in asthma etiology.[78]

6. Diet Dietary factors that affect the methylation process have also been found to affect disease risk through epigenetic mechanisms.[79] In the fetal development of mice, dietary supplementation with nutrients that tend to increase methylation ("methyl donors") such as folic acid, methionine, vitamin B_{12}, choline and betaine, increases DNA methylation.[80] In addition, the phytoestrogen genistein found in soy, while not a methyl donor, also has the effect of increasing DNA methylation through an unknown mechanism.[81] Conversely, diets lacking methionine, folate, or other methyl donors have been shown to lead to reduction in methylation across the entire genome in rats, producing an increase in tumor formation.[82] Another study demonstrated that reducing the availability of methyl donors such as folate acid and certain vitamin B compounds in the diet of adult female sheep resulted in offspring that were heavier and fatter than normal as adults, had elevated blood pressure, and were insulin resistant.[83] Excessive alcohol intake also has been shown to produce global reductions in methylation.[84] These findings suggest the need to continually reassess both the beneficial effects and the potential risks of many dietary supplements (e.g., folates) that could affect methylation patterns in future generations. Postnatal abnormal nutrition, such as caloric restriction diets, could affect gene imprinting and cause diabetic and uterine defects.[85]

The classic demonstration of epigenetic effects from diet comes from the *agouti* mouse, in which the coat color and health of offspring mice are dependent on maternal dietary methyl supplementation. Without maternal dietary supplementation, offspring tended to have yellow coats and obesity, and were prone to diabetes and cancer, whereas offspring of mothers which were given methyl supplements (including folate, L-methionine, and vitamin B_{12}) during a critical mid-stage of gestation tended to have agouti coats and were lean and non-diabetic.[86] Significantly, this epigenetic effect was not limited to the first-generation offspring, but was also passed on to the second generation, suggesting that a grandmother's diet might affect her grandchildren's health via an epigenetic mechanism.[87]

Some intriguing studies in human populations have reported evidence of such a transgenerational effect of nutritional status on subsequent generations. For example, in one study, the food availability for grandparents when they were 8 to 12 years old affected the longevity of their same-sex grandchildren, with scarcity of food for the grandparent being associated with longer life expectancy in their grandchildren of the same gender.[88]

7. In Vitro Fertilization Assisted reproductive procedures may disrupt imprinted genes during epigenetic reprogramming, especially in the presence of adverse environmental factors. As a therapy for male infertility, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) facilitates conception using abnormal sperm, which may contain imprinting defects.[89] However, the IVF/ICSI process may also lead to imprinting changes from exposure of the oocyte or developing embryo to exogenous factors in culture media.[90] Aberrant methylation of imprinted genes due to in vitro culture of embryos has been observed in sheep and rats.[91] Although no similar effects have been observed in human embryos, the clinical data on IVF babies has shown a six-fold increase in the incidence of Beckwith-Wiedemann

syndrome (BWS) in couples conceiving with IVF/ICSI, as well as an increased incidence of Angelman syndrome (AS).[92] BWS and AS are two rare diseases related to aberrant imprinting. Like other IVF/ICSI associated imprinting-related diseases, they are caused by maternal aberrant hypermethylation, suggesting a defect in the oocyte or a defect occurring during the time of fertilization and early embryo culture in the IVF/ICSI procedure.[93] Likewise, embryonic stem cells appear to be prone to epigenetic changes which could affect their stability and utility for therapeutic applications.[94]

Cloning animals using somatic cell nuclear transfer (SCNT), or potentially cloning humans in the future, may also involve aberrant epigenetic programming because the newly formed embryo's first key epigenetic period occurs shortly after fertilization, when the donor nucleus is being integrated into the denucleated oocyte during SCNT. According to the FDA, "[b]ecause preimplantation reprogramming occurs after fertilization, and in the case of nuclear transfer, after fusion of the donor nucleus with the oöplast, it is the most immediately affected by the cloning process, and may be most directly implicated in the development of clones with defects …The [FDA] assumes that if clones were to pose food consumption risks, the only mechanism by which those risks could arise would be from inappropriate epigenetic reprogramming, similar to those observed for other ARTs."[95]

8. Aging Aging remains the most complex phenotype studied so far. It has been well-documented that global methylation levels decrease in human tissues with the aging process,[96] and it has been suggested that reduction in methylation may be associated with a functional decline in learning and memory with age.[97] Identical twins born with identical genotypes increasingly diverge in their epigenetic profiles as they age, with the extent of divergence increasing as the twins got older, had different lifestyles, or spent less of their lives together.[98] "The cause of alterations in the pattern of DNA methylation during aging is not fully understood," but the data suggest that environmental factors modify epigenetic patterns to create different phenotypes from the same genotype.[99] Although the mechanism of these epigenetic changes accompanying aging remains poorly defined, it appears that these epigenetic alterations contribute to certain aging effects, including genomic instability, increased risk of cancer, and development of autoimmunity.[100]

9. Maternal Behavior There are intriguing suggestions that maternal behavior can induce epigenetic changes in offspring that affect health later in life. Perhaps the most dramatic studies are those showing that nurturing behavior by female rats to their offspring in the first week of life affected behavioral patterns in those offspring, with increased pup licking and grooming resulting in grown offspring that exhibit reduced fearfulness and better response to stress.[101] These maternal programming effects have been shown to be mediated by epigenetic changes including both DNA methylation and histone changes.[102] While these behavioral effects of early developmental epigenetic programming typically last the lifetime of the animal, subsequent studies have shown that the epigenetic effects and their behavioral consequences can be reversed with interventions involving dietary methyl supplementation.[103] As one review of these data summarized, "these findings indicate that early postnatal life experiences can modify behaviour by altering the epigenome, and that the inherent plasticity of the epigenome potentially allows for reversal in adulthood – an important finding in terms of possible therapeutic strategies."[104]

A growing body of data also suggest that maternal behavior in humans can affect the subsequent health of children via an epigenetic mechanism. For example, a recent study found that maternal stress, measured as medication for depression or anxiety during the early years of a child's life, increased the risk of asthma in those children later in life when they reach age seven.[105] The authors of this study concluded that their findings "are consistent with emerging evidence that maternal care alters stress responses in the offspring through an epigenetic model of inheritance."

D. Unique Aspects of Epigenetic Changes

Epigenetic changes are similar to genetic mutations in that they can both result in heritable changes in gene expression and function. In addition, there are several unique characteristics of epigenetic changes that differ from traditional genetic mutations, including the following.

- Epigenetic changes tend to occur at a much higher frequency than mutations in the DNA sequences.[106] For example, toxic agents acting through a genotoxic mechanism will usually only result in mutations in less than 0.01 percent of offspring,[107] whereas epigenetic processes often affect the majority of offspring.
- Epigenetic perturbations allow for much more rapid evolutionary change than traditional genetic mutations.[108] This potential for rapid variation permits a species to respond much more quickly to changes in environmental conditions.
- Susceptibility to epigenetic change is highly sensitive to the dose of relevant environmental agents, and also to the stage of development at which exposure occurs.[109] In particular, exposure at key stages of early development such as gastrulation and neonatal development are disproportionately prone to result in adverse response. The epigenetic state of an organism has a "lifecycle," whereas genotype does not, remaining constant throughout the organism's lifecycle.[110] Accordingly, "the nascent field of 'environmental epigenomics', must consider not only the magnitude but also the timing of exposure."[111]
- Genetic mutations tend to be irreversible, subject to reverse mutation only at extremely low frequencies, but epigenetic changes are intrinsically reversible.[112] This creates the opportunity for epigenetic interventions in the form of drugs or diet to restore normal epigenetic status, and suggests that diseases caused by epigenetic aberrations may be more easily treatable and preventable than diseases caused by more permanent genetic mutations.[113]
- Epigenetic changes tend to be tissue-specific, and thus can differ from one cell type to another within the same organism.[114] In contrast, germ-line genetic changes are generally stable and consistent throughout the tissues of an individual organism. This tissue-by-tissue variability of epigenetic alterations could have important practical effects, such as differential effects of drugs in different tissues.[115]
- Epigenetic changes also tend to be species-specific, so a carcinogenic or toxic response in a laboratory study using rodents may be less predictive of a similar risk for humans than such animal results produced by genotoxic or other traditional toxicological mechanisms.[116] Moreover, non-vertebrate species used in many toxicological assays have little or no methylation, making them inappropriate for evaluating epigenetic effects, even though they might be useful models for mutagenesis and other toxic effects.[117]

E. Questions Remaining to be Answered in Epigenetics Research

Epigenetics is an emerging field, especially as applied to humans. Aberrant DNA methylation profiles were first identified in human cancer about twenty-five years ago. Today, epigenetic regulation has been shown to be prevalent in the genome, and what is now known may only be the tip of the iceberg. From September 2006 to September 2007, more than 2500 articles were published in this field.[118] Numerous studies have found that many cancers and common diseases are regulated epigenetically as well as genetically.

At this point, scientists are unsure of how many substances cause epigenetic effects; what the degree of penetrance is for inherited epigenetic changes; what, if any, predispositions make individuals more susceptible to epigenetic alterations; whether tests will soon be available to identify epigenetic changes before they are manifested; and whether causal factors can be distinguished.[119] Ultimately, the answers to these questions rely on the decoding of the underlying mechanisms of epigenetic regulation related to age, diet, lifestyle, environmental toxicity exposure, and other unrevealed factors. Nevertheless, the gene-specific DNA methylation correlated with cancers and common diseases is now being investigated for potential use as biomarkers for molecular diagnosis, prognosis and prediction of biological aggressiveness and clinical responsiveness of disease treatment.

With retrospective studies of DNA methylation patterns and the availability of screening and analytical methods, the list of methylated genes as biomarker candidates is continuously expanding.[120] However, clinically applicable biomarkers to detect diseases are still limited. One notable finding is that a methylation biomarker for colorectal cancer has a seventy percent accuracy rate in detecting cancer in patients.[121] At the present time, there is no FDA approved DNA methylation-based molecular test kit for diagnostic purposes. Meanwhile, epigenetic therapies are being developed to reverse gene deactivation due to abnormal DNA methylation. The drug 5-azacytidine is the first FDA approved hypomethylating agent to treat myelodysplastic syndrome, a disease involving aberrant gene promoter hypermethylation events.[122]

III. LEGAL APPLICATIONS

In this section we explore the subset of legal issues most closely related to the unique scientific characteristics of epigenetics. In particular, we consider regulation, litigation, and discrimination.

A. Regulatory Applications

1. Environmental Regulation As awareness of the critical role of epigenetics in both normal and abnormal cell development has grown, so too has the realization of the potential importance of the disruption of epigenetic mechanisms as a toxicity mechanism and an environmental regulatory priority.[123] Many important toxic chemical hazards are now known or suspected to act, at least in part, by epigenetic mechanisms.[124] Examples include some endocrine disrupting chemicals such as certain pesticide and

plastic compounds,[125] and metals such as nickel,[126] cadmium,[127] and arsenic.[128] Most recently, relatively low-level exposures to bisphenol A, a compound used in many plastic products, was shown to cause epigenetic alterations in rats that may increase cancer risk.[129]

A number of federal environmental regulatory statutes require assessments for risks to human health that potentially implicate epigenetic effects, including the Clean Air Act (CAA),[130] the Clean Water Act (CWA),[131] the Toxic Substances Control Act (TSCA),[132] the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA),[133] the Resource Conservation and Recovery Act, (RCRA),[134] the Safe Drinking Water Act (SDWA)[135], and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[136]

The environmental statute most likely to first incorporate epigenetic assessments is FIFRA, as amended by the 1996 Food Quality Protection Act (FQPA), which regulates pesticide safety.[137] There are several aspects of FIFRA that would make this statute a particularly likely candidate for incorporating epigenetic data into risk assessment and regulatory decisions. First, FIFRA is the only federal environmental statute that requires pre-market safety testing and regulatory approval of chemical products, in this case pesticides. Before a pesticide can obtain regulatory approval to be commercially distributed, a prescribed battery of approximately 100 toxicology assays must be conducted and reported to the EPA in a process called "registration."[138] Although none of these assays currently directly evaluates epigenetic effects, it would be relatively straightforward to incorporate such an assay into the prescribed battery of tests. Second, the 1996 FQPA amendments require the EPA to develop a testing program for endocrine disruptor pesticides, which often involve epigenetic effects.[139] Finally, FQPA required the EPA to presumptively apply an extra ten-fold safety factor to protect children,[140] and again because epigenetic effects are expected to occur in early development, this new provision is also amenable to considering epigenetic influences.

Notwithstanding these provisions, the EPA has yet to take regulatory action or develop a risk assessment method based expressly on epigenetic risks under FIFRA or any other federal environmental statute. The potential for a significant epigenetic role in toxicity from many environmental exposures suggests that new assays may be needed in safety assessments to evaluate such effects. Direct assessment of epigenetic changes, such as the levels of DNA methylation, may be warranted in toxicity screening batteries such as those provided under FIFRA for pesticides. One recent review warned:

> *The fact that exposure of a mother to some common environmental agents can result in the persistent chemical modification of the genome of the offspring points out to the critical urgency for screening and identifying environmental epigenetic modifiers. Such agents would have escaped detection using classic assays for genotoxic agents and environmental hazards.*[141]

Other experts suggest that routine testing for methylation status may be premature, but that such assessments may be useful to consider on a case-by-case basis.[142] It has also been suggested that DNA methylation status may be useful as a biomarker of toxicity that could be used to screen individuals or organisms that have been exposed to toxic substances.[143] While DNA methylation is being used as a cancer biomarker, it has not yet been used as a biomarker for evaluating exposure to and risk from hazardous

substances.[144] Given the trans-generational nature of many epigenetic disruptions, transgenerational studies will be needed to evaluate some epigenetic-mediated toxicity. This has significant scientific, economic and legal implications. For example, insurance policy claims and tort liability may have a "long tail" if the toxic effects from agents acting via an epigenetic mechanism are not manifested until one or more generations into the future.

Such assays will raise critical issues about the definition of a toxic or "adverse" effect. Several environmental statutes, including both FIFRA and TSCA, require manufacturers to report data suggesting that their products may produce "adverse" effects. Are changes in DNA methylation alone, which may be or may not be associated with an increased risk of disease, an "adverse effect" that triggers regulatory activity? Some changes in DNA methylation occur naturally, without any association with toxicity, while others may be caused by toxic exposures but are transient and reversible.[145] Of course, other DNA methylation changes may indicate a significant toxicological response. As noted, the issue in trying to distinguish between innocuous and important methylation changes is similar to the issue involving changes in gene expression following environmental exposures, which sometimes may indicate the early stages of a disease process, but other times may simply be a reversible, adaptive response to the external stimulus.[146] For example, one recent study found that exposure to bisphenol-A, which has been found to cause toxic effects in some animal studies, caused epigenetic changes in the offspring of exposed mice but no apparent effects on reproductive outcomes, litter size, or offspring health.[147] Should such epigenetic effects in the absence of any other detectable toxicity response be considered an "adverse effect" for regulatory purposes? One policy response that has been suggested in the literature in the context of other molecular biomarkers would be only to treat as toxicologically significant those changes that have been shown to be related to or "anchored" to a known toxic response.[148]

The timing of exposure to toxic substances, not just the dose, also greatly impacts the potential for epigenetic effects.[149] In particular, exposures to the fetus during the gastrulation stage, or exposures to newborns, tend to be the most sensitive periods for inducing epigenetic effects. Traditional toxicology assays generally do not expose test animals in the fetal or newborn stages, and thus may miss important toxicity effects mediated through epigenetic mechanisms.[150] As the importance of epigenetic influences on toxicity emerges, it may therefore be necessary to expand the test periods for animal toxicity testing to include these sensitive periods.

Studies have also indicated that factors affecting epigenetic programming in early development can affect behavior.[151] It is therefore possible that early-life exposures to environmental toxins with epigenetic impacts could manifest in behavioral alterations later in life. Thus, it may be necessary to include behavioral testing in toxicological screening to detect and evaluate such epigenetic toxicity.[152]

Another complication of using epigenetic changes in toxicological evaluations is that epigenetic changes tend to be highly species-specific, so that extrapolation from laboratory animals to humans may be more uncertain than for most other toxicological markers.[153] This caveat is also shown in the bioinformatics study of the mouse genome, which predicts 600 imprinted genes, whereas only about 300 are predicted in humans. For example, the insulin-like growth factor 2 receptor (*IGF2R*) gene acts as a tumor suppressor that is imprinted in mice (i.e., there is only one active copy), whereas both copies of this gene are expressed in humans (i.e., there is no imprinting).[154] A toxic agent that causes cancer in

mice by knocking out the single active copy of the *IGF2R* gene in that species may cause cancer much more infrequently in humans with two active copies of the gene, both of which must be inactivated to achieve the same cancerous hazard.[155] Another problem is that non-vertebrate species used in some toxicity testing (including yeast, nematodes, and fruit flies) do not have significant DNA methylation, making them even less useful and less appropriate for evaluating epigenetic changes, even though such models are widely used for screening for other toxicological endpoints.[156]

Toxic environmental agents acting via an epigenetic mechanism may also be unique in terms of the potential for dietary or other interventions to mediate their harmful effects. As discussed above, epigenetic changes differ from traditional genetic changes in that they are more easily reversed. Studies suggesting that diets rich in methylating agents such as folate or genistein (found in soy) may reverse the effect of environmental agents that cause DNA hypomethylation.[157] For example, maternal dietary supplementation with methyl donors, such as folic acid, counteracted the epigenetic changes that had been induced by the chemical bisphenol-A.[158] Such possibilities open the door to expanding environmental policy approaches from simply preventing toxic exposures to also include interventions designed to mitigate the adverse effects of environmental exposures that have already occurred.

2. Food and Drug Regulation Epigenetic knowledge has many potential applications in health care, including both therapeutic and diagnostic uses. The Food and Drug Administration (FDA) regulates several categories of products including drugs, medical devices, biologics, foods, and cosmetics, for the most part under authority provided by the Federal Food, Drug and Cosmetic Act (FFDCA).[159] The statute provides different regulatory criteria for each product category. The product category most likely to be impacted by epigenetics is prescription pharmaceuticals, which are required by the FFDCA to be preapproved by the FDA as safe and effective before they can be marketed.[160] Epigenetic effects can play both a Dr. Jekyl and Mr. Hyde role in drug development and safety. On the one hand, a drug that induces unwanted epigenetic effects might result in unanticipated adverse effects, with both regulatory and liability repercussions. On the other hand, a drug may be designed to intentionally induce epigenetic changes to treat diseases with an epigenetic etiology. And yet other drugs may elicit epigenetic changes for which no demonstrable outcome can be documented.

Because epigenetic changes tend to be reversible,[161] there is considerable promise and opportunity for the development of epigenetic drugs to restore a healthy epigenetic status. At least three epigenetic drugs have already been approved by the FDA, and several more are now in clinical testing.[162] Given the prevalence within cells of epigenetic factors in both normal cell development and aberrant conditions, the use of an epigenetic drug that simply increases or decreases epigenetic effects such as methylation would be risky because it is likely to disrupt many other genes in addition to the target gene that is hypo- or hyper-methylated.[163] Therefore, drugs that more precisely target the methylation of specific genes, or affect the molecular pathway leading to the aberrant hypo- or hyper- methylation, are more promising.[164]

The tissue-specific nature of epigenetic effects, in which epigenetic changes may differ from tissue-to-tissue, may further complicate safety and efficacy testing of drugs. Drugs targeting or affected by epigenetic markers may be more or less effective or toxic in some tissues than others based on epigenetic status.[165] New toxicological assays or methods may be needed to address this possibility.[166]

Another potentially important implication of epigenetics in drug approval is the role of epigenetic factors in drug efficacy and resistance. For example, studies have indicated that hypermethylation of DNA may be involved in the development of resistance to certain cancer drugs.[167] This effect may be important both for the regulatory evaluation of drug efficacy and in developing more effective drugs.

Finally, the observation that early life experiences may alter epigenetic programming may also have implications for drug safety and approval.[168] Epigenetic changes to critical genes involved in drug response as a result of early life experiences could affect subsequent drug efficacy or toxicity in such individuals.[169] These effects and the potential impact on variation in drug response within a population may be another factor to consider in evaluating drug safety.[170] Biological response to drug treatment may also be influenced by transient epigenetic status in ways that can only be documented erratically, and that may contribute to inter-individual differences in drug response.

Epigenetic alterations, such as changes in methylation levels at specific gene locations, can also potentially be used as a diagnostic indicator for both disease detection and classification.[171] For example, the tight connection between methylation changes and human cancers suggests that abnormal methylation patterns could be a useful early biomarker of cancer before it can be clinically detected.[172] These methylation biomarkers can be detected in the blood, as well as other bodily fluids, including urine, sputum, and breast ductal lavage.[173] Early detection of individuals with epigenetic changes signifying a cancer risk can be used as a diagnostic measure for prevention:

> *Hopefully, we will move away from a view of preventive oncology focusing simply on nonspecific risk factors to identifying large numbers of patients showing altered epigenetic risk and targeting them for intervention…. By focusing on common changes in the population, present in apparently normal tissue before neoplasms arise, such approaches could have a substantial impact on cancer morbidity and mortality.*[174]

Similarly, detection of methylation changes that occurred in early development and predispose many individuals to late onset diseases, such as diabetes, hypertension, and Alzheimer's disease, could be very useful for diagnosing such diseases early, and even in facilitating prevention or treatment of such diseases *before* they are clinically detected.[175] DNA methylation patterns can also be used to classify disease, for example to subdivide tumors that were previously indistinguishable into separate subcategories that have different prognoses and treatment options.[176] Thus, epigenetic markers may be used for diagnosis, prognosis, and prediction of response to treatment.[177] Already, some companies have begun to offer commercial epigenetic tests for such purposes, which may require FDA approval.[178]

In addition to the pharmaceutical and diagnostic device applications of epigenetics, the FDA has recently confronted potential risks relating to epigenetics in its consideration of whether to approve food and milk from cloned animals. As stated previously, the FDA found that if cloned animals presented any food risks, they would probably be related to aberrant epigenetic programming of embryos created by somatic cell nuclear transfer cloning methods.[179] Notwithstanding concerns about potential epigenetic effects in cloned animals, the FDA concluded that meat and milk from cloned animals are safe. As the *Washington Post* summarized the 968 page FDA risk assessment of cloned animals released in January 2008:

> *Finally, there was the overarching problem of deciding which measures would best predict whether the food was safe. Most puzzling was whether to take into account the subtle alterations in gene activity, called epigenetic changes, that are common in clones as a result of having just one parent. In the end, facing the reality that epigenetics have never been a factor in assessing the wholesomeness of food, agency scientists decided to use the same simple but effective standard used by farmers since the dawn of agriculture: If a farm animal appears in all respects to be healthy, then presume that food from that animal is safe to eat.*[180]

While the FDA did not allow potential epigenetic effects to block approval of the sale of products from cloned animals, the FDA will no doubt focus its attention on epigenetic effects in continuing to monitor this issue.

3. Occupational Safety and Health Regulation The Occupational Safety and Health Act of 1970 (the Act)[181] is the principal federal law regulating workplace safety and health.[182] The Act, applicable to all employers engaged in a business affecting interstate commerce,[183] applies to an estimated six million workplaces and 90 million employees.[184] Pursuant to Section 18 of the Act,[185] twenty-three jurisdictions have received federal approval for state occupational safety and health plans, which operate to divest the federal government of jurisdiction and replace it with state oversight containing similar requirements of demonstrated effectiveness.[186] The Act is enforced by the Assistant Secretary of Labor for Occupational Safety and Health, who serves as administrator of the Occupational Safety and Health Administration (OSHA).

The Act requires covered employers to provide to each employee a workplace "free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees."[187] This "general duty clause" may be used as the basis of an enforcement action brought by the Secretary of Labor ("Secretary") only when no duly promulgated occupational safety and health standard applies to the alleged violative conditions.[188] The other main statutory duty of covered employers is to comply with all applicable occupational safety and health standards promulgated by the Secretary pursuant to Section 6 of the Act.[189] The failure to comply with either the general duty clause or OSHA standards may result in the Secretary issuing a citation[190] and assessing a range of civil and criminal penalties[191] depending on the categorization and gravity of the violation and other factors.[192]

Section 6(b)(5) of the Act prescribes the substantive requirements for promulgation of standards regulating toxic substances and harmful physical agents.[193] This section of the Act is likely to be the focus of regulators if the issue of epigenetic effects is considered a proper subject for OSHA rulemaking. The first issue is whether OSHA authority extends to the regulation of epigenetic effects, especially when these effects can be preclinical and subclinical as well as clinical. Section 6(b)(5) provides that in promulgating standards for toxic substances or harmful physical agents:

> *The Secretary …shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life.*[194]

Do epigenetic effects constitute "material impairment of health or functional capacity" if the exposure has not yet caused any symptoms in the exposed employee? This question has not yet been considered explicitly by the courts. In one case, *United Steelworkers of America v. Marshall*,[195] the court analyzed in a different context whether the Act authorized the Secretary to regulate the subclinical effects of occupational exposures. In reviewing the lead standard, the D.C. Circuit held that the Secretary had established that lead exposure causes subclinical hematological, neurological, renal, and reproductive effects, that these effects are causally related to clinical lead disease, and therefore that the subclinical effects constitute "material impairment."[196] Applying this precedent, it would appear that some epigenetic effects could be considered a material impairment and thus subject to regulation under the Act. Nevertheless, OSHA would have to demonstrate that the subclinical epigenetic effects are causally related to clinical effects.

Although the scientific literature on epigenetic effects in humans is still quite sparse, it is possible that individuals have varied epigenetic responses to exposure to occupational toxins. Thus, another question to address is whether the Act requires protecting the most sensitive employees. The language of section 6(b)(5), quoted above, provides that "no employee will suffer material impairment of health." Despite this seemingly absolute language, the Supreme Court has held that the Act does not require regulation to the level of zero risk.[197] In *Industrial Union Dep't, AFL-CIO v. American Petrolium Institute*,[198] the plurality opinion stated that "the statute was not designed to require employers to provide absolutely risk-free workplaces whenever it is technologically feasible to do so …[but] was intended to require the elimination, as far as feasible, of significant risks of harm."[199] Nevertheless, the plurality supported the concept of "action level" medical surveillance of employees exposed below the permissible exposure level because surveillance "could ensure that workers who were unusually susceptible …could be removed from exposure before they had suffered any permanent damage."[200]

Other possible strategies to reduce epigenetic effects include two types of medical surveillance: pre-exposure testing for individual susceptibility to epigenetic changes and post-exposure monitoring of exposed workers to detect epigenetic effects of exposure.[201] Epigenetic testing in the workplace is likely to be as controversial as genetic testing.[202] The use of genetic testing in the workplace has the potential to invade privacy, undermine individual autonomy, create stigma and psychological harms, and possibly lead to discrimination against the individual and his or her family members.[203] The above discussion is compounded by the fact that diet alone can change the epigenome. Accordingly, no workplace genetic or epigenetic testing program should be considered without overwhelming scientific evidence of its necessity and efficacy as well as the absence of alternatives. It would be a mistake, however, to prohibit genetic and epigenetic testing in all instances and for all purposes. Epigenetic testing might be appropriate if it were provided on an optional basis to applicants and employees and the results were available only to the individual.[204] Then, the applicant or employee could decide whether his or her particularized risks from exposure were acceptable.

The Genetic Information Nondiscrmination Act of 2008 (GINA)[205] prohibits employers from discriminating against an employee (including an applicant) on the basis of genetic information, or requesting, requiring, or purchasing genetic information about an employee or a family member of the employee.[206] Employees are generally prohibited from acquiring genetic information, but an exception applies where the information is used for genetic monitoring of the effects of toxic substances if (1)

written notice is provided to the employee; (2) the employee provides voluntary, written authorization or the monitoring is required by law; (3) the employee is informed of individual results; (4) the monitoring is in compliance with applicable regulations; and (5) the employer receives results only in aggregate form.[207] The same general approach should be applied to monitoring for epigenetic effects of toxic exposures.

One last issue to consider is the possible transgenerational effects of epigenetic changes. Regulation under the Act is not absolute, and it involves considering various factors, such as the severity of the risk, the likelihood of the risk, the latency of the risk, the feasibility of controlling the hazards, and the economic consequences of regulation. It remains to be seen whether the possibility of transgenerational epigenetic effects from certain exposures will be a significant factor influencing increased workplace safety and health regulation.

B. Litigation Applications

Epigenetic effects caused by chemicals and other environmental agents may provide a new source of litigation and liability under the common law. Such litigation, especially when it involves second and third generation effects, would raise a number of novel challenges and issues. For example, how should statute of limitations rules be applied? Another issue involves obtaining discovery of medical records of other family members, including the parents or grandparents who were initially exposed.

The leading precedent for this type of claim is the litigation concerning DES, which was used widely over a twenty-four year period until it was found in 1971 to cause severe reproductive illnesses in daughters of pregnant women who took the drug. “DES was manufactured by a variety of companies, and many different types of DES tablets made by different manufacturers were interchanged freely.”[208] Product liability actions were brought against the manufacturers of DES by daughters of women who ingested it. Although the cases raised numerous legal issues, such as the plaintiffs’ ability to recover despite the inability to identify the manufacturer or manufacturers of the pills taken by the plaintiffs’ mother, the courts and legislatures of many states showed a great willingness to overcome the structural or procedural barriers to recovery.[209] However, the third-generation DES claims brought by the granddaughters of the women who took DES have not been successful due primarily to the courts’ unwillingness as a matter of tort theory and public policy to extend liability to victims who have a relationship too distant or attenuated from the actual tortious action (“victim attenuation”).[210]

McMahon v. Eli Lilly & Co.[211] is the first reported appellate decision involving a third-generation DES claim. The plaintiff mother had several children born prematurely and one premature infant died.[212] The parents (“plaintiffs”) sued the defendant-drug company claiming that the mother’s in utero exposure to DES when her mother (the maternal grandmother) ingested the drug produced by the defendant was the cause of the death of their infant son.[213] The court reversed the lower court’s grant of defendant’s directed verdict, based in part on the plaintiffs’ failure to make a *prima facie* showing that the defendant manufactured the drug to which the mother was exposed.[214] The court held that the evidence showing that the defendant was the wholesale supplier of DES to the drug store where the drug was obtained by the maternal grandmother of the deceased infant was sufficient to establish culpability.[215] The court also stated that the lower court’s requirement of the foreseeability by the defendant of the specific risk

to the third generation was far too narrow.[216] The court found that medical research was then published and reported experiments showing that DES could cause physical abnormalities in the reproductive tracts of animals exposed to the drug in utero.[217] The court reasoned that these reports explicitly suggested the drug's potential dangers to humans as well as animals.[218] The court thus concluded that this evidence was more than sufficient to support a jury verdict for the plaintiffs.[219] Therefore, the court reversed the directed verdict for the defendant and remanded the case for a new trial.[220] This ruling was much more favorable to the third-generation DES claimant than subsequent decisions from other courts.

To avoid injustice in DES litigation, the New York legislature and the New York Court of Appeals removed legal barriers to tort recovery in DES-daughter cases for the special circumstances in the DES context.[221] In 1986, the legislature amended the law to provide that the limitations period in exposure cases begins upon discovery of the injury instead of upon the exposure.[222] In 1989, the New York Court of Appeals held, in *Hymowitz v. Eli Lilly & Co.*, that liability could be imposed upon DES manufacturers based on their share of the national DES market, notwithstanding the plaintiff's inability to identify the particular manufacturer at fault for her injuries.[223]

In *Enright v. Eli Lilly & Co*., the same court stated that:

> *[The] recent developments demonstrate legislative and judicial solicitude for the victims of DES, but they do not establish DES plaintiffs as a favored class for whose benefit all traditional limitations on tort liability must give way. To the extent that special rules have been fashioned, they are a response to unique procedural barriers and problems of proof peculiar to DES litigation.*[224]

The court suggested that removing such a legal barrier in the context of third-generation DES cases would affect the substantive law of tort; therefore, the court refused, largely based on policy considerations, to extend the strict products liability recovery to third generation plaintiffs.[225]

In *Enright*, the court treated the DES-granddaughter injury as a "preconception tort" committed against the mother, and thus precluded the tort claim based on the bright-line "no duty rule"[226] developed in *Albala v. City of New York*.[227] However, as in *Albala*, the *Enright* court stated that to recognize a cause of action on behalf of the DES-granddaughter "would require the extension of traditional tort concepts beyond manageable bounds."[228] Further, the court in *Enright* stated that "[l]imiting liability to those who ingested the drug or were exposed to it in utero serves this purpose."[229] Implicitly, these holdings suggest that the court considered that the relevant injury was to the mother and the DES-daughter, but not to the later-conceived grandchild, thus undercutting the duty of care to the DES-granddaughter altogether.

Among a score of unsuccessful third-generation DES cases in different jurisdictions,[230] the *Enright* case is the most controversial in that it is the least consistent with its jurisdiction's DES and proximate cause precedents, where the court had allowed for recovery of proximate injuries, but not remote ones.[231] The court used the policy argument of needing to put some limits on liability to draw the line between the second and third generations, without explaining why it did not draw the line between the

third and fourth generations.[232] In *Enright*, the court "seemed to have difficulty deciding where to draw the line between proximate and remote consequences, between properly compensating victims and not holding drug manufacturers liable in perpetuity."[233] "The types of injuries at issue here are not ones that involve multigenerational genetic damages. Instead, they are a direct result of the compensable injuries to the DES-daughters. In denying [their] recovery …, the New York Court of Appeals ignored traditional doctrines that impose reasonable limitations on tort liability while compensating plaintiffs directly injured by defendants."[234] Further, Judge Hancock stated that if it was foreseeable that the DES-daughter's in utero exposure might cause defects in her reproductive system, "[c]learly it cannot be said as a matter of law" that it was not foreseeable that the DES-granddaughter would be born with injuries.[235]

In *Grover v. Eli Lilly & Co.*, an Ohio Supreme Court third-generation-DES case, the court decided that "[a] pharmaceutical company's liability for the distribution or manufacture of a defective prescription drug does not extend to persons who were never exposed to the drug, either directly or *in utero*."[236] This decision also has been criticized. Justice Resnick stated in his dissenting opinion:

> *What could have a more direct causal connection than a premature birth by a woman who was known to have an incompetent cervix? From this it becomes readily apparent that DES grandchildren were a foreseeable group of plaintiffs. It can hardly be argued that there is no duty owed to a foreseeable plaintiff.*[237]
>
> *Finally, as John B. Maynard succinctly summarized:*
>
> *Once the tired old arguments about the opening of the floodgates of litigation are stripped away; once the sound justification for imposing a reasonable duty of care on drug manufacturers is recognized; and once the exaggerations about the inhibitions of medical researchers are put in perspective, it should be the law that the third-generation-DES claim presents a valid cause of action deserving of a remedy.*[238]

Third-generation DES claims have not been successful due to the courts' interpretation of a victim attenuation problem in the 1980s. However, with the emergence of epigenetics; the acceptance of epigenetics' hypothetical role as an added layer of regulation in genetic common diseases (CDGE, Common Disease Genetic and Epigenetic hypothesis),[239] or more broadly, the recognition that P (phenotype) = G (Genes) + E (Environment) + EpiG (Epigenetics)),[240] the "attenuation problem" in the DES-granddaughter tort claims may deserve a reevaluation based on the gradual discovery of underlying mechanisms of transgenerational epigenetic diseases.

C. Discrimination in Employment Against Fertile Women

Human susceptibility to epigenetic insults varies over the course of a lifetime, with increased vulnerability occurring, among other times, in utero.[241] Thus, the issue is raised whether some employers could prohibit fertile women from working where there is exposure to substances suspected of causing epigenetic harms. The purpose of such exclusion would be to prevent harms to the later-born children

of female employees and to reduce the likelihood of personal injury claims brought by those children based on their in utero exposure.[242] Adverse health effects also might extend to the offspring of the prenatally exposed children and, conceivably, even to future generations.

Similar employment discrimination concerns already have been addressed in the context of maternal exposure to teratogenic substances in the workplace.[243] In *UAW v. Johnson Controls, Inc.*, the employer was concerned about its possible liability if a pregnant employee was occupationally exposed to inorganic lead and later gave birth to a child with congenital defects caused by the mother's work-place exposure.[244] Under the metabolic stress of pregnancy, lead stored in the mother's bones may be released into her bloodstream and then into the fetus.[245] Thus, female employees could transmit lead to a developing fetus from preconception exposures.[246] Furthermore, the fetus is most sensitive to lead exposure in the early stages of pregnancy, when many women do not even know they are pregnant.[247]

Because of the possible health risks to the fetus and financial risks to the company, Johnson Controls adopted a "fetal protection policy" that barred all fertile women – regardless of their marital status, reproductive plans, or other considerations – from any job likely to elevate their blood lead above a certain level.[248] The Supreme Court held that that the employer's policy constituted sex discrimination in violation of Title VII of the Civil Rights Act of 1964.[249] The Court held that by excluding only women with childbearing capacity from jobs with lead exposure, the employer's policy was explicit, disparate treatment discrimination, which could only be upheld by applying a bona fide occupational qualification (BFOQ) defense.[250]

The Court interpreted the statutory defense of BFOQ under Title VII as narrow.[251] It permits discrimination based on gender only in limited circumstances where discrimination is "'reasonably necessary' to the 'normal operation' of the 'particular' business."[252] Although safety concerns may establish a BFOQ, "the safety exception is limited to instances in which sex or pregnancy actually interferes with the employee's ability to perform the job."[253] Because fertile women were capable of performing the job, the Court concluded that the employer failed to establish the BFOQ defense.[254] Of particular relevance to transgenerational epigenetics, the Court said that concerns about the welfare of the next generation did not establish a BFOQ of female sterility. "Decisions about the welfare of future children must be left to the parents who conceive, bear, support, and raise them rather than to the employers who hire those parents."[255]

In the years since the Court's decision in *Johnson Controls*, new scientific discoveries have documented the significant risks from early life exposures, including prenatal exposures, to various toxic substances. Among the risks associated with certain early exposures are neurological harms,[256] cardiovascular harms,[257] and increased risk of cancer.[258] Will the multigenerational harms implicated by epigenetics lead to a reconsideration of the *Johnson Controls* preference for worker autonomy over employer paternalism and the desire to protect future generations? Although the health of future generations – both proximate and remote – is a vital consideration, increased transparency and vigilance with regard to occupational health hazards is preferable to authorizing vast exclusionary practices affecting female applicants and employees. Some of the methods of protecting against transgenerational harms of any etiology or manifestation are substitution of substances, improved environmental controls, personal pro-

tective equipment, medical surveillance, optional and confidential fertility and pregnancy testing, and optional medical removal with maintenance of pay and benefits for workers who are or are attempting to become pregnant.[259]

D. Other Forms of Discrimination

Many other claims for alleged epigenetics-based discrimination are possible. In the employment setting, the first issue is whether an epigenetic mark or the predisposition to epigenetic changes constitutes a disability under the Americans with Disabilities Act (ADA)[260] or its state analogs.[261] Applying current case law, it is unlikely that a court would hold that an epigenetic change or predisposition to an epigenetic change is an impairment that constitutes a "substantial limitation of a major life activity."[262] In *Sutton v. United Air Lines, Inc.*,[263] the Supreme Court adopted a narrow view of the coverage of the ADA. The Court observed that the ADA's findings section[264] specifically states that "some 43,000,000 Americans have one or more physical or mental disabilities, and this number is increasing as the population as a whole is growing older."[265] Thus, the Court reasoned that the ADA was not intended to cover individuals whose impairments may be mitigated through the use of eyeglasses and other corrective measures. Similar reasoning would undermine the claim that an asymptomatic individual with an epigenetic change is an individual with a disability under the ADA.[266]

Two-thirds of the states have enacted laws prohibiting genetic discrimination in employment.[267] At the federal level, the recently enacted Genetic Information Nondiscrimination Act (GINA)[268] prohibits discrimination in employment on the basis of genetic information. Although state laws differ in their definition of genetic information, many state enactments are similar to GINA, which defines genetic information as "information about [an] individual's genetic tests, the genetic tests of family members of such individual, and the manifestation of a disease or disorder in family members of such individual."[269] Scientifically, epigenetic information is *not* genetic information, and therefore it probably would be necessary to amend state and federal nondiscrimination laws to prohibit discrimination based on epigenetic factors.[270] Consequently, an employer concerned about possible epigenetic effects on employees perceived to be susceptible to occupational exposures could simply refuse to employ the individual or assign the individual to other tasks. Clearly, genetic non-discrimination laws should be amended or new legislation should be enacted to prohibit such practices.

There are also many possible uses of epigenetic information in insurance underwriting. The vast majority of states have enacted laws prohibiting genetic discrimination in health insurance.[271] At the federal level, GINA prohibits discrimination in health insurance on the basis of genetic information. The state and federal approaches vary in their coverage and definitions, but, as with the employment discrimination laws discussed above, none of the laws are likely to cover epigenetic conditions.[272] Epigenetic information might be used to predict future health in any of the myriad situations where genetic information is now used or where there is concern about possible use, such as life insurance,[273] disability insurance,[274] and long-term care insurance.[275]

The discovery of epigenetic effects in humans further undermines the viability of genetic-specific nondiscrimination legislation. Legislation prohibiting the inappropriate use of predictive health information is more logical from a scientific and policy standpoint because it focuses on the effect of future

health risks on current opportunities rather than on the biological mechanism by which the harm may be manifested.

IV. ETHICAL IMPLICATIONS

As a relatively new field of research, epigenetics has the potential to raise a variety of issues related to research ethics, such as conflicts of interest, research integrity, informed consent, and privacy. As scientists apply epigenetics to human health, concerns about clinical ethics and public health ethics are likely to arise. It is not clear if or how the epigenetic applications of these issues will differ from the well-considered context of clinical genetics or public health genetics. Therefore, in this section we have chosen to focus on the unique ethical implications of epigenetics in the following broad areas: environmental justice, privacy and confidentiality, access to health care, intergenerational equity, and eugenics.

A. Environmental Justice

Toxic chemicals, airborne pollutants, pesticides, diesel exhaust, tobacco smoke, and other harmful exposures are not distributed randomly throughout society.[276] The exposures are frequently linked with poverty, discriminatory land use, and substandard living and working conditions.[277] Populations exposed to environmental insults also are more likely to have pre-existing health conditions, often with poor clinical management.[278] As discussed previously, some common environmental exposures may have epigenetic effects.[279] Assuming that epigenetic changes adversely affect the most vulnerable segments of society, it could be argued that there is a heightened moral obligation to remediate the environmental sources of risk and prevent future harmful exposures. On the other hand, if the most vulnerable people are considered at greatest risk, as a practical matter, the political resolve of policy makers might be lessened.[280]

"Environmental justice refers to a political and social movement to address the disparate distribution of environmental harms and benefits in our society, and to reform the processes of environmental decision making so that all affected communities have a right to meaningful participation."[281] The debate over environmental justice raises important distributive issues for environmental law,[282] and it has led to great controversy. Claims about environmental justice have been termed "unsettling" to supporters of strong environmental protection because they "sound disturbingly reminiscent of accusations of elitism that environmental activists have long heard and long discounted."[283] Thus, there may be a tension between some traditional environmentalists and advocates of environmental justice.[284] More overt critics of environmental justice have asserted that claims for environmental justice lack empirical foundations[285] and that there is little evidence to support the claim of disproportionate burdens on minorities because "locally undesirable land uses are attributable largely to the workings of the market."[286]

The environmental justice movement began in the 1970s and 1980s with civic activism, protests, and litigation.[287] In the 1990s, two events gave it major impetus. First, in 1992, the EPA published the report of a workshop on environmental equity that concluded that minorities experienced disproportionately greater exposure to environmental pollutants.[288] Later that year, the EPA created the Office of Environmental Equity (the name was later changed to the Office of Environmental Justice) to oversee

environmental justice at the agency.[289] Second, in 1994, President Clinton issued an executive order requiring all federal agencies to make environmental justice part of their mission by identifying and addressing, as appropriate, "disproportionately high and adverse human health or environmental effects" of its programs, policies, and activities "on minority populations and low-income populations."[290]

Epigenetics could change the traditional environmental justice analysis in three important ways. First, in some cases it could shift the focus from populations receiving disproportionate exposure to those with greater susceptibility. Second, rather than focusing on geographically defined communities, it concentrates on the individual biological factors that establish increased risk. Third, it does not directly address the differential exposures caused by race and ethnicity, although some epigenetic marks have different frequencies in certain subpopulations.[291]

In addition, viewing environmental epigenetics in light of environmental justice raises the issue of whether it is prudent to concentrate on the problems of vulnerable populations when there are global concerns. According to one line of reasoning:

> *If we are unable to solve globally pressing problems such as ozone depletion, climate change, or the loss of biodiversity, we might not have an environment, or a planet, left that is hospitable to human society. Without an effective and expeditious solution to such larger problems, there will be nothing left for racial minorities or the poor to live in, or for that matter anyone else.*[292]

Nevertheless, the global scale of overall environmental challenges should not divert attention from addressing environmental injustices,[293] especially when the harms associated with exposures threaten the health of future generations in a self-perpetuating cycle of poor health and reduced quality of life.

There are no easy solutions to the problems of environmental justice, which must be considered along with the other "emerging ideals" of environmental policy–sustainable development, ecosystem management, and pollution prevention.[294] Environmental justice also is related to economic justice, human rights, social equality, and public health.[295] It remains to be seen whether emerging scientific evidence of epigenetic effects, including transgenerational effects, will be a catalyst for environmental justice.

B. Privacy and Confidentiality

Epigenetics could create a wealth of sensitive information about an individual's likelihood of developing health problems in the future and possibly transmitting the risk to his or her offspring. More sensitive health information is likely to lead to greater concerns about privacy and confidentiality protections at a time when interoperable networks of health information exchange will make widespread disclosure of health information increasingly easy.[296]

"Health information privacy refers to an individual's right to control the acquisition, uses, or disclosures of his or her identifiable health data."[297] Individuals have various privacy interests with regard to epigenetic information. If they undergo testing to determine whether they have developed epigenetic

changes based on environmental exposures, they may want to prevent disclosure of the information to third parties, such as employers and insurers, as well as to friends, relatives, and even some health care providers. Among the issues raised are whether any restrictions may be placed on an individual's desire for privacy; whether individuals have a moral or legal duty to warn other at-risk individuals, including family members; and if some exposed individuals prefer not to undergo testing, especially when there is no medical intervention, whether they should have a right not to know.[298]

"Confidentiality, which is closely related [to privacy], refers to the obligations of those who receive information to respect the privacy interests of those to which the data relate."[299] It is the basis of professional standards of conduct and legal obligations.[300] Issues surrounding confidentiality include determining what standard should be used in assessing an individual's consent or authorization for disclosure and whether the standard should vary based on the nature of the disclosure. Also, in what situations, such as public health emergencies, should disclosure take place in the absence of an individual's permission to disclose health information or even over the individual's objection?

These issues have been discussed in the literature on genetic privacy and confidentiality,[301] and a threshold question is whether the ethical analysis of epigenetic information varies from the analysis of genetic information. Because the answer may be more a matter of social policy than science, it may be too soon to answer inasmuch as it is not clear what degree of stigma will attach to epigenetic data. Although epigenetic information and genetic information have many of the same attributes, they are not identical. For example, epigenetic effects are environmentally induced and thus they might be viewed as less stigmatizing because the source of the problem is not "bad genes." They also may be reversible. On the other hand, because of possible transgenerational effects, epigenetics may be viewed the same as genetics. Finally, there is simply the matter of semantics. Many policy makers and lay people will incorrectly assume that epigenetics is just a type of genetics.

Another ethical issue to consider is whether or how to segregate or otherwise restrict access to certain sensitive information when health information is disclosed in electronic format for treatment or other purposes. Several countries developing electronic health information networks are also developing systems to isolate or mask certain data elements (e.g., clinical encounters, diagnoses) or categories of health information (e.g., reproductive health, substance abuse, mental health).[302] Although masking certain sensitive health information will help protect individual privacy and confidentiality, classifying certain health information as especially sensitive might further stigmatize the information and result in a self-fulfilling prophecy. It remains to be seen whether masking technologies or comparable methods will be adopted in the United States and, if so, whether individuals will have the option to mask genetic or epigenetic information from disclosure.[303]

C. Equitable Access to Health Care

Greater understanding of the link between environmental exposures and epigenetic effects will increase the importance of exposed individuals receiving health services for prevention, monitoring, and treatment. Unfortunately, many of the individuals most likely to live and work with hazardous exposures (e.g., indigent, minority, and alien populations) are among the least likely individuals to have regular,

timely, and comprehensive access to health care.[304] Thus, the issue of access to health care for individuals exposed to substances causing or likely to cause epigenetic harms is merely a subset of the issue of access to health care for vulnerable populations.

In 2006, 47.0 million Americans under the age of sixty-five, 15.8 percent of the population, were estimated to be without health insurance.[305] The percentage of uninsured for non-Hispanic white persons was 10.8 percent, for Black persons was 19.0 percent, and for Hispanic persons was 34.1 percent.[306] Since 1985, the federal government has declared its commitment to redressing disparities in health care access and health status for racial and ethnic minorities in the United States.[307] After over two decades of special emphasis on eliminating health disparities, however, wide and persistent gaps in health status and access to health care remain.[308]

Numerous moral arguments have been made in support of the notion that the richest nation on Earth should join the rest of the industrialized world in providing access to health care for all of its residents.[309] One of the most powerful arguments is that access to health care promotes justice by preventing health problems that would impair the functioning of healthy individuals and by restoring unhealthy individuals to a condition comparable to the societal norm.

> *To be sure, health care does many things for people: it extends life, reduces suffering, provides information and assurance, and in other ways improves the quality of life. Nevertheless, it has one general function of overriding importance for purposes of justice: it maintains, restores, or compensates for the loss of (in short, protects) functioning that is normal for a member of our species.*[310]

These arguments lead to the following proposition: A just society ought to provide universal access to health care because it is a per se good and because it is an instrumental good that facilitates a range of opportunities for human flourishing.

Considering access to health care in light of transgenerational epigenetic harms, which may be self-perpetuating and especially affect vulnerable populations, the following proposition emerges: A just society ought not permit future generations to experience the debilitating health effects caused by current environmental exposures when the health effects are known or knowable and the environmental conditions are preventable or remediable.

In addition to environmental remediation, individual prevention, monitoring, and treatment are the three main ways in which medical intervention could ameliorate the effects of harmful environmental exposures. The availability of preventive services is likely to be closely related to access to health care generally. Medical monitoring may be valuable when there are known exposures and effective treatments at the preclinical or clinical stage. Medical monitoring has been used as a remedy in toxic tort litigation,[311] and it also would be an appropriate intervention for public health agencies. It is too soon to tell what treatment modalities would be effective for epigenetic environmental insults, but widespread adoption of treatment measures may be politically challenging and is likely to depend on cost and efficacy. Thus far, with regard to genetics, rather than epigenetics, both public and private payers have been reluctant to approve payment for many clinical genetic services on the grounds that they are experimen-

tal or not medically necessary.[312] Furthermore, the current health care system is designed more to treat individuals when they are ill than to provide prevention and wellness services for individuals to maintain their good health.[313]

D. Intergenerational Equity

Intergenerational equity, or justice between generations, involves "the inherent relationship that each generation has to other generations, past and future, in using the common patrimony of natural and cultural resources of our planet."[314] According to this principle, each generation is considered a custodian of the planet for future generations.[315] Intergenerational equity requires accommodating the often-conflicting interests of current and future generations. For example, global climate change is caused in large part by carbon dioxide emissions. The benefits of carbon dioxide emissions, in terms of current power generation, are reaped exclusively by the current generation, but the burdens are borne by both the current and future generations. "The lifetime of carbon dioxide in the upper atmosphere is over 100 years, so that the full (cumulative) effects of current emissions will not be felt until the beginning of the twenty-second century."[316] Thus, apart from the concerns of the current generation about pollution and climate change in the near term, to what degree should concerns about the planetary conditions of remote, future generations influence contemporary decisions?

Intergenerational equity has been applied to many of the vexing environmental issues of our time, including the disposal of nuclear waste,[317] extinction of species of plants and animals,[318] climate change,[319] overpopulation,[320] and destruction of natural resources.[321] Nevertheless, it is difficult to articulate with any precision the nature of the duty to future generations or the process by which such considerations are part of current policy deliberations.[322] According to Edith Brown Weiss, one of the leading theorists of intergenerational equity, there are three key principles: (1) each generation should be required to conserve the diversity of the natural and cultural resource base; (2) each generation should be required to maintain the quality of the planet so that it is passed on in no worse condition than the present generation received it; and (3) each generation should provide its members with equitable rights of access to the legacy from past generations and should conserve this access for future generations.[323]

If humankind has a responsibility to future generations to refrain from activities that cause environmental harms to the planet, including damaging current and future generations of wildlife, then it follows that the responsibility also extends to environmental harms that could damage the genomes and epigenomes of future generations of humans. The Universal Declaration on the Human Genome and Human Rights provides: "The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity."[324] Similar reasoning would apply to the human epigenome. Furthermore, the human genome and epigenome are not static,[325] and the relationship between changes caused by natural biological processes and those caused by the built environment[326] has not yet been explored to any substantial degree.

There is no widely accepted ethical argument with regard to inter-generational equity and the human epigenome. There are however, numerous questions to consider, including: (1) how to characterize the nature of the duty; (2) for how many generations does an epigenetic effect have to persist to implicate intergenerational equity; (3) how do the severity, type, duration, and reversibility of the harm affect inter-generational equity; (4) how should the harm's effect on individuals, families, cultures, and humanity be assessed; (5) what effect does recognition of intergenerational equity concerns and epigenetic processes have on contemporary environmental policies; and (6) how does the existence of transgenerational epigenetic effects relate to intragenerational equity?

The refinement of philosophical analyses of transgenerational environmental epigenetics will be greatly influenced by scientific developments and the emerging understanding of biological mechanisms. It is not too soon, however, to analyze the fundamental values underlying the issues. In 1943, in his haunting and prescient monograph, *The Abolition of Man*, C.S. Lewis wrote:

> *Each generation exercises power over its successors: and each, in so far as it modifies the environment bequeathed to it and rebels against tradition, resists and limits the power of its predecessors. This modifies the picture which is sometimes painted of a progressive emancipation from tradition and a progressive control of natural processes resulting in a continual increase of human power. In reality, of course, if any one age really attains, by eugenics and scientific education, the power to make its descendants what it pleases, all men who live after it are the patients of that power. They are weaker, not stronger: for though we may have put wonderful machines in their hands we have pre-ordained how they are to use them. And if, as is almost certain, the age which had thus attained maximum power over posterity were also the age most emancipated from tradition, it would be engaged in reducing the power of its predecessors almost as drastically as that of its successors.*[327]

Lewis was specifically addressing the intergenerational implications of genetic enhancement or positive eugenics. Nevertheless, his comments are also applicable to transgenerational harms to the genome and epigenome. Any current generation – through design or through negligence in permitting hazardous exposures – that alters the biological inheritance of its successors has "pre-ordained" the lives of future generations in meaningful ways. The current generation will have weakened future generations, limited their options, and required them to pay with their health or their lives for the environmental misdeeds of their forebears.

E. Eugenics

The moral imperative to consider the transgenerational effects of environmentally-induced epigenetic changes suggests the following intergenerational genetic and epigenetic principle: Each generation should maintain the quality of the human genome and epigenome and pass it on in no worse condition than the present generation received it. Although such a principle is consonant with intergenerational equity generally and is appealing in the abstract, its application must be carefully circumscribed or it could lead to eugenic policies.

Eugenics is the Original Sin of modern genetics. As initially formulated by Francis Galton and his early followers, eugenics was a humane, progressive, and scientific enterprise with the goal of improving humanity by increasing the number of genetically well-endowed individuals and decreasing the number of genetically disfavored.[328] In the first third of the twentieth century, the primary governmentally-imposed method of negative eugenics was to reduce the number of genetic "defectives" through involuntary sterilization.[329] Although certain physical defects were considered "genetic," there was a significant emphasis on eliminating the "genetic defects" of promiscuity, shiftlessness, pauperism, and other traits without a genetic basis.[330] Thus, eugenic measures were based on flawed science, and the horrendous social policy brought about by eugenics soon spun out of control, reaching a low point in Nazi Germany.[331] "Genetically undesirable" also became equated with "socially or politically undesirable" and sterilization quickly led to genocide.[332] In the United States, eugenics was epitomized by compulsory sterilization laws enacted in thirty states that resulted in the sterilization of 60,000 individuals.[333]

Eugenics has been thoroughly discredited since the end of World War II as bad and often disingenuous science leading to disastrous social policy. Yet, the repeal of laws authorizing coercive governmental measures should not be equated with the complete absence of eugenics today. Sociologist Troy Duster has written that social pressures to avoid the birth of children with congenital disabilities has increased and will continue to increase prenatal diagnosis and abortion, a situation he terms "backdoor eugenics."[334] Philosopher Philip Kitcher calls *laissez-faire* eugenics the current practice of limited, optional prenatal genetic testing and utopian eugenics the availability of these services to all citizens.[335]

The routine use of prenatal genetic testing and selective abortion has been criticized on other grounds, as well. The feminist critique argues that the ability to terminate pregnancies when the fetus has a genetic anomaly leads to the objectification of women's procreative capacity.[336] It also threatens to redefine motherhood by depersonalizing the experience of pregnancy and forcing women to decide what quality of life is worth living.[337] The disability rights critique argues that abortion because of a fetal genetic anomaly is based on the erroneous assumption that a disability precludes living a meaningful life.[338] Such attitudes also adversely affect the lives of individuals with disabilities because their quality of life depends on educational, employment, and similar societal opportunities.[339]

In light of the controversy surrounding expanded prenatal testing for genetic disorders, it is important to consider whether similar concerns would be raised about prenatal testing for epigenetic effects. It is possible that preconception, preimplantation, and prenatal testing for epigenetic alterations could be developed and used as a way to prevent the transmission of transgenerational epigenetic harms. The prospect of adverse health conditions persisting through several generations is likely to increase the social pressure on prospective parents to prevent the transmission of epigenetic effects. Thus, once epigenetic testing and pregnancy avoidance or termination become an option for prospective parents, epigenetic harms could become highly stigmatized and the moral responsibility could shift from those entities responsible for the environmental exposures to the parents who failed to respond "appropriately" to the risk by preventing or terminating the pregnancy.[340]

Whenever individuals' reproductive decisions attempt to alter the biological makeup of their offspring, the claim has been made that they are interfering with the natural order and attempting to "play God."[341] The notion that current generations should be resolute in not influencing the biology of their

progeny, however, is inconsistent with the basic goals of modern medicine – quite apart from reproductive technologies. For example, pediatric medical interventions that save the lives of genetically impaired children have the effect of permitting these children to reach the age of reproduction and thereby transmit their genetic risk of impairment to future generations. The fact that saving the lives of children afflicted with genetic disorders will burden the gene pool is a morally insufficient reason to withhold beneficial treatment. As the eminent population geneticist Theodosius Dobzhansky wrote: "[I]f we enable the weak and the deformed to live and to propagate their kinds, we face the prospect of a genetic twilight; but if we let them die or suffer when we can save them[,] we face the certainty of a moral twilight."[342]

Although concerns about eugenic implications should remain an important consideration in evaluating policies and practices with transgenerational genomic and epigenetic effects, the fear of eugenics should not invariably override the obligations to future generations. Philosopher Allen Buchanan and his colleagues have written: "Reprehensible as much of the eugenic program was, there is something unobjectionable and perhaps even morally required in the part of its motivation that sought to endow future generations with genes that might enable their lives to go better."[343] The moral imperative to act is even stronger when the intervention prevents the acquiring of deleterious transgenerational alterations and thus involves preventing their lives from being worse.

V. CONCLUSION

Epigenetics is an exciting new avenue of scientific exploration that already has demonstrated that certain exposures, especially during periods of developmental vulnerability, can cause long-term harms to exposed individuals and sometimes their progeny. Epigenetics invalidates the assumption that nature and nurture operate as independent forces in influencing human development and disease.

Numerous legal and ethical issues are raised by epigenetics, especially regarding individual and societal responsibilities to prevent hazardous exposures, monitor health status, and provide care. Epigenetics represents a new class of biological effects from harmful exposures and adds a multigenerational dimension to environmentally-caused adverse health effects. Epigenetics serves to highlight the effects of inequality in living and working conditions, as well as a range of disparities in access to health care and other societal opportunities.

Another social challenge is that epigenetics establishes an additional basis of individual biological variation. Although many societies are only beginning to deal with the legal and ethical implications of human genetic variation,[344] epigenetics adds another layer of complexity to individual variability. Epigenetics also adds another class of sensitive health information in need of privacy protection and another basis for possible stigmatization and discrimination. Individuals and society will be challenged to respond to these new measures of acquired human variation with policies based on the ethical principles of respect for persons, beneficence, privacy, and justice.

Finally, epigenetics raises difficult questions about the obligations of society to preserve the soundness of the human genome and epigenome for the benefit of future generations. In developing a principle of intergenerational equity for the human genome and epigenome, optimum social policy lies between in-

difference to the health burdens of future generations and eugenic notions of manipulating heredity to improve the human condition. The ultimate policy challenge will be to move beyond the formulation of principles that recognize these aims to devising feasible strategies to achieve them.

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132. 15 U.S.C. §§ 2601–2629 (2000).

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134. 42 U.S.C. §§ 6901–6992k (2000).

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136. 7 U.S.C. §§ 136(a)-(y) (2000).

137. Food Quality Protection Act of 1996, Pub. L. No. 104–170, 110 Stat. 1489 (codified as amended in scattered sections of 7 U.S.C. and 21 U.S.C.).

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139. 21 U.S.C. § 346a(p).

140. 21 U.S.C. § 346a(b)(2)(C)(ii)(II).

141. Szyf, *supra* note 14, at 16.

142. Watson & Goodman, *supra* note 11, at 14.

143. Sutherland & Costa, *supra* note 10, at 156.

144. Szyf, *supra* note 14, at 10.

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146. *See* Gary E. Marchant, *Genomics and Toxic Substances: Part I - Toxicogenomics*, 33 Envtl. L. Rep. 10071, 10089 (2003).

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150. *See* Carl Cranor, *The Legal Failure to Prevent Subclinical Developmental Toxicity*, 102 Basic Clin. Pharmacology & Toxicology 267, 271 (2008) (arguing for testing of substances for developmental toxicity focusing on the timing of in utero and postnatal exposures). The National Toxicology Program has recently begun to include newborn exposure in its chronic carcinogenicity studies, which it had not routinely done previously, but still does not include prenatal exposures. Thayer Kristina A, Foster Paul M. Workgroup Report: National Toxicology Program Workshop on Hormonally Induced Reproductive Tumors – Relevance of Rodent Bioassays. *115 Envtl Health Persp.* 2007;1351:1355. [PMC free article] [PubMed] [Google Scholar].

151. *See supra* notes 19, 35–37 and accompanying text.

152. Szyf, *supra* note 14, at 17–18.

153. Jirtle & Skinner, *supra* note 26, at 253–62. (explaining that "[u]nderstanding how the environment influences human health and disease will ultimately require a comprehensive knowledge of the human epigenome, because the epigenome …varies markedly between species").

154. Id.

155. *Id.* at 253–62.

156. Szyf, *supra* note 14, at 10.

157. Jirtle & Skinner, *supra* note 26, at 255.

158. *See* Dolinoy et al., *supra* note 129, at 13059.

159. 21 U.S.C. § 301–397 (2000).

160. 21 U.S.C. § 355(d) (2000).

161. *See supra* notes 109, 143 and accompanying text.

162. Egger Gerda, et al. Epigenetics in Human Disease and Prospects for Epigenetic Therapy. *429 Nature.* 2004;457:460. [PubMed] [Google Scholar]; Interlandi Jeneen. Chemo Control, : Drugs Target Epigenetic Changes in Cancer Cells. *Sci Am, April.* 2007;24:24. [Google Scholar]; Szyf, *supra* note 14, at 8. Approved drugs that operate by an epigenetic mechanism include two that inhibit methylation (Vidaza in 2004 and Dacogen in 2006) that were approved to treat myelodysplastic syndrome, a blood disorder that can progress to leukemia, and one drug that enhances acetylation, Zolinza, which was approved in 2006 to treat T cell lymphoma.

163. Feinberg Andrew P. An Epigenetic Approach to Cancer Etiology. *13 Cancer J.* 2007;70:73. [PubMed] [Google Scholar]

164. Id.

165. Feinberg, *supra* note 23, at 433–40.

166. Szyf, *supra* note 14, at 8.

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169. *Id.* at 17.

170. *Id.* at 8, 17.

171. Verma Mukesh, Manne Upender. Genetic and Epigenetic Biomarkers in Cancer Diagnosis and Identifying High Risk Populations. *60 Critical Rev Oncology/Hematology.* 2006;9:13. [PubMed] [Google Scholar]

172. *See* Herceg & Hainaut, *supra* note 28, at 33.

173. Id.

174. Feinberg, *supra* note 163, at 73.

175. Jirtle & Skinner, *supra* note 26, at 261.

176. Gal-Yam Einav Nili, et al. Cancer Epigenetics: Modifications, Screening and Therapy. *59 Ann Rev Med.* 2008;267:274. [PubMed] [Google Scholar]; Esteller, *supra* note 47, at 1155.

177. Esteller, *supra* note 47, at 1155.

178. *See* Press Release, OncoMethylome Sciences, OncoMethylome Science to Profile DNA for Abbott Onocology Compounds (Dec. 17, 2007) (stating that its "tests are designed to help the physician (i) accurately detect cancer in early stages of cancer development, (ii) predict a patient's response to drug therapy, and (iii) predict the likelihood of cancer recurrence."), *available at* http://www.oncomethylome.com/newsroom/pressrelease2007_detail.php?version=2&id=aHR0cDovL2N3cy5odWdpbm9ubGluZS5jb20vTy8xMzczMTQvUFIvMjAwNzEyLzExNzY0NzUueG1s; *see also* Epigenomics, Biomarker Services, http://www.epigenomics.com/en/biomarker_services/ (last visited Oct. 20, 2008). Another company marketing epigenetic biomarkers is Epigenomics AG (*see* www.epigenomics.com).

179. *See supra* note 95 and accompanying text.

180. Rick Weiss, *FDA Says Clones Are Safe for Food – Report Finds No Evidence of Risks*, Wash. Post, Jan. 15, 2008, at A1.

181. 29 U.S.C. §§ 651–78 (2000).

182. The Federal Mine Safety and Health Act, 30 U.S.C. §§ 801–965 (2000), regulates mines, and several other laws regulate workplace safety and health in specific industries. *See* Mark A. Rothstein, Occupational Safety and Health Law § 2:15 (2008).

183. 29 U.S.C. § 652(5).

184. Rothstein, *supra* note 182, § 1:4, at 8.

185. 29 U.S.C. § 667.

186. Rothstein, *supra* note 182, § 3:2, at 52, § 3:10, at 63. The state plans cover private sector employers as well as state and local government employers, the latter of which are excluded from coverage under the federal Act. *Id.* at 22–25, 49–63.

187. 29 U.S.C. § 654(a)(1).

188. Safeway, Inc. v. OSHRC, 382 F.3d 1189, 1194 (10th Cir. 2004). *See* Rothstein, *supra* note 182, §5:35, at 230–31.

189. 29 U.S.C. § 654(a)(2).

190. 29 U.S.C. § 658.

191. 29 U.S.C. § 666.

192. Rothstein, *supra* note 182, §§ 14:9–15.

193. 29 U.S.C. § 655(b)(5).

194. Id.

195. United Steelworkers of America, AFL-CIO-CLC v. Marshall, 647 F.2d 1189 (D.C. Cir. 1980).

196. *Id.* at 1252–59.

197. *See generally* Mark A. Rothstein, *Occupational Health and Discrimination Issues Raised by Toxicogenomics in the Workplace*, Genomics and Environmental Regulation 183, 186–87(Gary E. Marchant, Richard R. Sharp, & Jamie Grodsky eds. 2008).

198. Indus. Union Dep't, AFL-CIO v. Am. Petroleum Inst., 448 U.S. 607 (1980).

199. *Id.* at 641.

200. *Id.* at 658.

201. The use of post-exposure surveillance probably would require pre-exposure testing, as well, to establish a baseline for comparison.

202. On the issue of genetic testing and genetic discrimination in employment, *compare* Clegg Roger, Abbott Bragdon v. Asymptomatic Genetic Conditions, and Antidiscrimination Law: A Conservative Approach. *3 J Health Care L & Pol'y.* 2000:409. [PubMed] [Google Scholar], Dichter MarkS, Sutor Sarah E. The New Genetic Age: Do Our Genes Make Us Disabled Individuals Under the Americans with Disabilities Act? *42 Vill L Rev.* 1997;613 [PubMed] [Google Scholar], and Epstein Richard A. The Legal Regulation of Genetic Discrimination: Old Responses to New Technology. *74 BU L Rev.* 1994;1 [PubMed] [Google Scholar] (supporting the use of genetic testing), *with* Greely Henry T. Genotype Discrimination: The Complex Case for Some Legislative Protection. *149 U Pa L Rev.* 2001;1483 [PubMed] [Google Scholar] (explaining that "[t]he federal government should prohibit some uses of genetic information in decisions by employers and health insurers …."), Deborah Gridley, Note, *Genetic Testing under the ADA: A Case for Protection from Employment Discrimination*, 89 Geo. L.J. 973 (2001), *and* Pauline Kim, *Genetic Discrimination, Genetic Privacy: Rethinking Employee Protections for a Brave New Workplace*, 96 Nw. U.L. Rev. 1497 (2002) (opposing genetic testing).

203. *See* Brandt-Rauf Paul W, Brandt-Rauf Sherry I. Genetic Testing in the Workplace: Ethical, Legal, and Social Implications. *25 Ann Rev Pub Health.* 2004;139:141. [PubMed] [Google Scholar]; McCunney Robert J. Genetic Testing: Ethical Implications in the Work-place. *17 Occup Med.* 2002;665:668–69. [PubMed] [Google Scholar].

204. The following guidelines, adapted from recommendations regarding genetic testing in the workplace, would appear to have equal force in the context of epigenetic testing.
1. Employers have a duty to inform applicants and employees of genetic markers of increased risk based on occupational exposures.
2. Individuals should have the option of undergoing genetic testing for these markers at the employer's expense.
3. The testing should be performed by a physician of the individual's choosing.
4. The results should be available only to the individual.
5. The significance of both a positive and a negative test should be explained to the individual.
6. The choice of whether to accept the job should be left to the individual.
7. Only in the rare situations where employment of the individual would constitute a direct, immediate, and severe threat to self or others would the employer be justified in performing its own genetic testing and excluding the individual. Mark A. Rothstein, *Genetics and the Work Force of the Next Hundred Years*, 2000 Colum. Bus. L. Rev. 371, 395 (2000).

205. Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110–223, 122 Stat. 881. For a further discussion of GINA, *see infra* notes 278–280 and accompanying text.

206. 42 U.S.C.S. §§ 2000ff-1(a)-(b) (LexisNexis 2008).

207. *Id.* § 2000ff-1(b)(5)(E).

208. Wenger Kaimipono David. Causation and Attenuation in the Slavery Reparations Debate. *40 USF L Rev.* 2006;279:314. [Google Scholar]

209. Batt Tracey I. DES Third-Generation Liability: A Proximate Cause. *18 Cardozo L Rev.* 1996;1217:1223–29. [Google Scholar] (the barriers include statutes of limitations, identification of the particular manufacturer, and jurisdiction over the defendants).

210. Wenger, *supra* note 208, at 306–07 (discussing the most commonly contested issues in mass tort litigation that includes the potential but attenuated connection between the victims, the extent of harm, and the culpability of the alleged wrongdoers. Further, identifying a responsible manufacturer from among a pool in a large market creates a problem of wrongdoer attenuation, connecting a harm to later victims, such as children and grandchildren, of the original product consumer creates a problem of victim attenuation and establishing the causal connection between the wrongdoer's product and the later victim's harm faces a problem of act attenuation).

211. 774 F.2d 830 (7th Cir. 1985).

212. *Id*. at 832.

213. *Id.* at 831–32.

214. *Id.* at 832, 834.

215. *Id.* at 832–34.

216. *Id.* at 835. ("This ruling frames the question of foreseeability far too narrowly. Under Illinois precedent, to prevail on a failure to warn claim, a plaintiff must show 'that the manufacturer knew or should have known of the danger presented by the use or consumption of the product' and that the manufacturer did not warn of the product's 'dangerous propensities.' Plaintiffs need not prove that Lilly should have anticipated the precise injuries allegedly suffered, so long as the injuries lay within the scope of the known dangerous propensities of DES." (quoting Woodill v. Parke Davis & Co., 402 N.E.2d 194, 198 (Ill. 1980))); *Id.* at 835 n.7 ("[The plaintiff]'s treating physician, an expert witness, testified that it was 'more likely than not' that [her] injuries were caused by prenatal exposure to DES. This testimony was sufficient to allow the jury to consider the question.").

217. *Id.* at 834.

218. Id.

219. *Id.* at 835–36.

220. *Id.* at 838.

221. Hymowitz v. Eli Lilly & Co., 539 N.E.2d 1069, 1080 (N.Y. 1989) (explaining that "DES victims were prejudiced under current law" and that "[t]he Legislature does not violate equal protection by providing a rational piecemeal remedy for what may be a larger problem").

222. *Id.* at 1079.

223. *Id.* at 1075.

224. 570 N.E.2d 198, 201–02 (N.Y. 1991).

225. *Id.* at 204.

226. *Id.* at 201.

227. Albala v. City of N.Y., 429 N.E.2d 786, 787 (N.Y. 1981). In *Albala*, the child was born with brain damage allegedly attributable to the defendants' negligence in perforating the mother's uterus in the course of an abortion four years earlier.

228. Id.

229. *Enright*, 570 N.E.2d at 203.

230. In addition to New York, several other jurisdictions have rejected third-generation DES injury cases using various and divergent theories. *See* Sorrells v. Eli Lilly & Co., 737 F. Supp. 678 (D.D.C. 1990) (holding that manufacturer owed no duty under Maryland law, which at this time does not extend to unborn granddaughter of person who had ingested DES); DeMayo v. Schmitt, 5 Pa. D. & C. 4th 197, 200 (Pa. Com. Pl. 1989) (rejecting strict liability claims, but suggesting negligence claims may be viable in appropriate circumstances).

231. *Enright*, 570 N.E.2d at 206 (Hancock, Jr., J., dissenting).

232. *Id*. at 203.

233. Batt, s*upra* note 209, at 1242.

234. Id.

235. Id.

236. Grover v. Eli Lilly & Co., 591 N.E.2d 696, 700–01 (Ohio 1992).

237. *Id.* at 703 (Resnick, J. dissenting).

238. Maynard John B. Third-Generation-DES Claims. *27 New Eng L Rev.* 1992;241:285. [Google Scholar]

239. Feinberg, *supra* note 23, 438.

240. Petronis Arturas. Epigenetics and Twins: Three Variations on the Theme. *22 Trends Genetics.* 2006;347:348. [PubMed] [Google Scholar]

241. Jirtle & Skinner, *supra* note 26, at 253–62 (discussing study results that support the hypothesis of "fetal basis" or "developmental origins of adult-onset disease," a theory supported by increasing evidence that "environmental influences early in development are linked to disease phenotypes through modifications of the epigenome").

242. Although the employee-mother would be barred by workers' compensation from bringing a personal injury action for the injuries caused by her own exposure, the child of an employee may not be prohibited from bringing an action based on in utero exposure. *Compare* Snyder v. Michael's Stores, Inc., 945 P.2d 781 (Cal. 1997); Omori v. Jowa Hawaii Co., Ltd., 981 P.2d 714 (Haw. Ct. App.), *aff'd as mod'd*, 981 P.2d 703 (Haw. 1999); and Cushing v. Time Saver Stores, Inc., 552 So. 2d 730 (La. Ct. App. 1989) (action not barred by workers' compensation) *with* Widera v. Ettco Wire & Cable, 611 N.Y.S.2d 569 (App. Div. 1994), *appeal denied*, 626 N.Y.S.2d 755 (1995) (employer owed no duty to child in utero).

243. In humans, the most sensitive period for birth defects caused by *in utero* exposure to teratogens is generally considered between weeks two and 12 of gestation. David Eaton, *Toxicology, in* Textbook of Clinical Occupational and Environmental Medicine 83, 89 (Linda Rosenstock et al. eds., 2005).

244. 499 U.S. 187, 190–92 (1991).

245. Jacqueline M. Moline & Philip J. Landrigan, *Lead*, *in* Textbook of Clinical Occupational and Environmental Medicine 967, 971 (Linda Rosen-stock et al. eds. 2005).

246. Id.

247. *See* Welch Laura S. Decisionmaking About Reproductive Hazards. *1 Sem Occup Med.* 1986;97:105. [Google Scholar]

248. *UAW*, 499 U.S. at 191–92.

249. *See UAW,* 499 U.S. at 211.

250. *UAW*, 499 U.S. at 200.

251. *Id.* at 201. Section 703(e) of Title VII provides, in pertinent part, that "it shall not be an unlawful employment practice for an employer to hire and employ employees …on the basis of his religion, sex, or national origin in those certain instances where religion, sex, or national origin is a bona fide occupational qualification reasonably necessary to the normal operation of that particular business or enterprise …" 42 U.S.C. § 2000e-2(e) (2000).

252. *Int'l Union*, 499 U.S. at 201.

253. *Id.* at 204.

254. *Id.* at 206.

255. Id.

256. Rice Deborah, Barone Stan., Jr Critical Periods of Vulnerability for the Developing Nervous System: Evidence from Humans and Animal Models. *108 Envtl Health Persp (Supp 3)* 2000;511 passim. [PMC free article] [PubMed] [Google Scholar]

257. *See* Barker David JP. Fetal Programming of Coronary Heart Disease. *13 Trends in Endocrinology & Metabolism.* 2002;364:364. [PubMed] [Google Scholar].

258. *See* Barton Hugh A, et al. Assessing Susceptibility from Early-Life Exposure to Carcinogens. *113 Envtl Health Persp.* 2005;1125:1125. [PMC free article] [PubMed] [Google Scholar]; *see also* Cook Jennifer D, et al. Interaction Between Genetic Susceptibility and Early-Life Environmental Exposure Determines Tumor-Suppressor-Gene Penetrance. *102 Proc Nat'l Acad Sci.* 2005:8644. [PMC free article] [PubMed] [Google Scholar].

259. *See generally* Elaine Draper, *Reproductive Hazards and Fetal Exclusion Policies After* Johnson Controls, 12 Stan. L. & Pol'y Rev. 117 (2001) ("Greater awareness of reproductive hazards, along with new technologies for detecting them, can indeed serve useful ends in improving public health.").

260. 42 U.S.C. §§ 12101–12213 (2000).

261. Virtually every state has enacted a law prohibiting discrimination in employment on the basis of disability. Mark A. Rothstein et al., Employment Law § 3.15 (3d ed. 2004).

262. 42 U.S.C. §12102(2) defines "disability" as: "(A) a physical or mental impairment that substantially limits one or more of the major life activities of such individual; (B) a record of such an impairment; or (C) being regarded as having such an impairment." 42 U.S.C. § 12102(2) (2000).

263. Sutton v. United Airlines, Inc., 527 U.S. 471 (1999).

264. 42 U.S.C. § 12101(a)(1).

265. *Sutton*, 527 U.S. at 484 (quoting 42 U.S.C. § 12101(a)(1)). *See generally* Ruth Colker, *The Mythic 43 Million Americans with Disabilities*, 49 Wm. & Mary L. Rev. 1 (2007) (discussing the Court's interaction with Congress and the limits of the ADA's disability discrimination protections).

266. Another line of ADA cases makes it clear that minor or temporary impairments are not covered under the statute. *See, e.g.,* Chanda v. Engelhard/ICC, 234 F.3d 1219 (11th Cir. 2000) (holding employee's tendonitis did not substantially limit his performance of manual tasks); Leisen v. City of Shelbyville, 153 F.3d 805 (7th Cir. 1998) (depression); Kelly v. Drexel Univ., 94 F.3d 102 (3d Cir. 1996) (post-traumatic degenerative joint disease, which caused moderate difficulty walking or climbing stairs).

267. For an updated list of all state laws, see Nat'l Conference of State Legislatures, State Genetics Employment Laws, http://www.ncsl.org/programs/health/genetics/ndiscrim.htm (last visited Oct. 21, 2008).

268. Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110–223, 122 Stat. 881. *See* Rothstein Mark A. Putting the Genetic Information Nondiscrimination Act in Context. *10 Genetics in Med.* 2008:655. [PubMed] [Google Scholar].

269. 42 U.S.C.S. §2000ff(4)(A) (LexisNexis 2008).

270. Even if such legislation were seriously considered, it may not be effective if it uses the same approach as GINA, because current laws do not prohibit the disclosure of detailed clinical records (which might contain genetic or epigenetic information) pursuant to a compelled authorization after a conditional offer of employment. *See* Rothstein Mark A, Talbott Meghan K. Compelled Disclosure of Health Information: Protecting Against the Greatest Potential Threat to Privacy. *295 JAMA*. 2006;2882:2882. [PubMed] [Google Scholar]. Furthermore, it is difficult to justify affording special treatment to genetic or epigenetic information than other predictive health information. *See* Rothstein Mark A. Genetic Exceptionalism and Legislative Pragmatism. *Hastings Center Rep.* 2005 July-Aug;27:31–32. [Google Scholar].

271. For an updated list of all state laws, see Nat'l Conference of State Legislatures, Genetics and Health Insurance State Anti-Discrimination Laws, http://www.ncsl.org/programs/health/genetics/ndishlth.htm (last visited Oct. 25, 2008).

272. A significant limitation on the effectiveness of these laws is that they only prohibit discrimination against individuals who are asymptomatic. If an individual becomes affected, then the health insurance company may decline to renew or may increase the cost of the policy to the degree permitted by state insurance laws. For employment-based group health plans, the Health Insurance Portability and Accountability Act (HIPAA), prohibits any discrepancy in pricing or coverage based on health condition. 42 U.S.C. § 300gg-1(a)(1) (2000). This significant shortcoming underscores the need for more comprehensive approaches. *See* Rothstein, *supra* note 268, at 655–56.

273. *See generally* Genetics and Life Insurance: Medical Underwriting and Social Policy (Mark A. Rothstein ed., 2004) (exploring the proper policies for using genetic information in life insurance coverage determinations).

274. *See generally* Symposium, *Genetic Testing and Disability Insurance*, 35 J.L. Med. & Ethics (Special Supp.) 5 (2007) (providing the first ever in-depth study of genetic testing and disability insurance, through various essays written by a diverse group of experts, including scholars in law, health care, ethics, public policy, public health, and professionals from the insurance industry).

275. *See* Zick Cathleen D, et al. Genetic Testing for Alzheimer's Disease and its Impact on Insurance Purchasing Behavior. *24 Health Affairs.* 2005;483:483. [PMC free article] [PubMed] [Google Scholar] (stating that "[i]f genetic testing for Alzheimer's risk assessment becomes common, it could trigger adverse selection in long-term care insurance").

276. *See generally* The Quest for Environmental Justice: Human Rights and The Politics of Pollution (Robert D. Bullard ed., Sierra Club Books 2005) (discussing the disparate impact of environmental pollution on minorities and the poor).

277. Id.

278. *See generally* Richard G. Wilkinson, Unhealthy Societies: The Afflictions of Inequality (1996) (discussing pathways through which inequality and loss of social cohesion are likely to affect health).

279. See *supra* notes 66–84, 101–05 and accompanying text.

280. *See* Williams Robert W. Environmental Injustice in America and Its Politics of Scale. *18 Pol Geog.* 1999:49–73. [Google Scholar] (discussing politics of environmental justice).

281. Rechtschaffen Clifford. Advancing Environmental Justice Norms. *37 UC Davis L Rev.* 2003;95:96. [Google Scholar]. The EPA uses the following definition: "Environmental Justice is the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies." U.S. Environmental Protection Agency, Environmental Justice, http://www.epa.gov/compliance/environmentaljustice (last visited Oct. 24, 2008). *See generally* David Schlossber G. *Defining Environmental Justice: Theories, Movements, and Nature.* Oxford Univ. Press; 2007. [Google Scholar] (arguing that any definition of environmental justice needs "a broadly accessible, plural, and workable frame."). Environmental justice also has been referred to as environmental racism and environmental equity. Torres Gerald. Environmental Justice: The Legal Meaning of a Social Movement. *15 JL & Com.* 1996;597:603. [Google Scholar].

282. Richard J. Lazarus, Essay, *Fairness in Environmental Law*, 27 Envtl. L. 705, 715 (1997).

283. *Id.* at 714.

284. *But see* Peter Wenz, *Does Environmentalism Promote Injustice for the Poor?* In Environmental Justice and Environmentalism: The Social Justice Challenge to the Environmental Movement 57–83 (Ronald Sandler & Phaedra C. Pezzullo eds., 2007).

285. Bowen William. An Analytical Review of Environmental Justice Research: What Do We Really Know? *29 Envtl Mgmt.* 2002;3 [PubMed] [Google Scholar]

286. Torres, *supra* note 281, at 607. Vicki Been, *Locally Undesirable Land Uses in Minority Neighborhoods: Disproportionate Siting or Market Dynamics?*, 103 Yale L.J. 1383 (1994), *quoted in* Torres, *supra* note 281. *Contra* Pastor Manuel, Jr, Sadd Jim, Hipp John. Which Came First? Toxic Facilities, Minority Move-in, and Environmental Justice. *23 J Urb Aff.* 2001;1:1–21. [Google Scholar] (finding that minorities attract toxic storage and disposal facilities).

287. Yang Tseming. Melding Civil Rights and Environmentalism: Finding Environmental Justice's Place in Environmental Regulation. *26 Harv Envtl L Rev.* 2002;1:4–8. [Google Scholar]

288. Envtl. Protection Agency, Office of Policy Planning and Evaluation, Environmental Equity: Reducing Risk for All Communities, 12 (1992). *See* Yamamoto Eric K, Lyman Jen-L W. Racializing Environmental Justice. *72 U Colo L Rev.* 2001;311:318. [Google Scholar].

289. *See* Office of Environmental Justice, http://www.epa.gov/compliance/environmentaljustice (last visited Aug, 15, 2008).

290. Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations, Exec. Order No. 12,898, 59 Fed. Reg. 7,629 (Feb. 16, 1994).

291. *See* Marchant Gary E, Grodsky Jamie A. Genomics and Environmental Justice: Some Preliminary Thoughts. In: Sharp Richard R, Marchant Gary E, Grodsky Jamie A., editors. *Genomics and Environmental Regulation.* 2008. [Google Scholar] (recognizing these distinctions between traditional environmental justice analysis and environmental justice influenced by genetic susceptibility).

292. Yang, *supra* note 287, at 30.

293. Environmental justice is a global concern. *See* Claudio Luz. Standing on Principle: The Global Push for Environmental Justice. *115 Envtl Health Persp.* 2007:A 501. [PMC free article] [PubMed] [Google Scholar] (summarizing the environmental justice movement).

294. Torres, *supra* note 281, at 617.

295. *See, e.g.,* Lee Charles. Environmental Justice: Building a Unified Vision of Health and the Environment. *110 Envtl Health Persp (Supp 2)* 2002:141. [PMC free article] [PubMed] [Google Scholar].

296. *See* Mark A. Rothstein, *Protecting Privacy and Confidentiality in the Nationwide Health Information Network*, *in* Paper Kills: Transforming Health and Healthcare with Information Technology 17 (David Merritt ed., 2007).

297. Comm. on the Disposition of the Air Force Health Study Bd. on Population Health & Pub. Health Practice, Inst. of Med. of the Nat'l Academies, Disposition of the Air Force Health Study 115 (2006) [hereinafter Comm. on Population Health & Pub. Health Practice] (emphasis omitted).

298. *See generally* The Right to Know and the Right Not to Know (Ruth M. Chadwick et al. eds., Avebury 1997); Andorno R. The Right Not to Know: An Autonomy Based Approach. *30 J Med Ethics.* 2004;435:36. [PMC free article] [PubMed] [Google Scholar].

299. Comm. on Population Health & Pub. Health Practice, *supra* note 297, at 115 (emphasis omitted).

300. *See* Baruch A. Brody et al., Medical Ethics: Analysis of the Codes, Opinions, *and* Statements 161–233 (2001).

301. *See, e.g.,* Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era (Mark A. Rothstein ed., 1997); Rothstein Mark A. Keeping Your Genes Private. *Sci Am.* 2008 Sept.:64. [PubMed] [Google Scholar].

302. Joy Pritts & Kathleen Connor, The Implementation of E-Consent Mechanisms in Three Countries: Canada, England, and the Netherlands (2007), *available at* http://ihcrp.georgetown.edu/pdfs/prittse-consent.pdf.

303. *See* Letter from Simon P. Cohen, Chairman, Nat'l Comm. On Vital and Health Statistics, to the Honorable Michael O. Leavitt, Secretary, U.S. Dept. of Health and Human Services (Feb. 20, 2008), *available at* http://www.ncvhs.hhs.gov. Masking technology applies to the disclosure of health information for treatment purposes. "Contextual access criteria" refers to technology used to limit the disclosure of unnecessarily broad health information to third parties, such as employers and life insurers. *See* Rothstein & Talbott, *supra* note 270, at 2884.

304. See Hadley Jack. Sicker and Poorer – The Consequences of Being Uninsured: A Review of the Research on the Relationship Between Health Insurance, Medical Care Use, Health, Work, and Income. *60 Med Care Res & Rev (Supp)* 2003;3:38–41. [PubMed] [Google Scholar].

305. Press Release, U.S. Census Bureau, Household Income Rises, Poverty Rate Declines, Number of Uninsured Up (Aug. 28, 2007), *available at* www.census.gov/Press-Release/www/releases/archives/income_wealth/010583.html.

306. Id.

307. U.S. Department of Health and Human Services, Report of the Secretary's Task Force on Black & Minority Health, 1–2 (1985), *available at* http://www.omhrc.gov/assets/pdf/checked/ANDERSON.pdf.

308. *See* Comm. on Understanding & Eliminating Racial & Ethnic Disparities in Health Care, Inst. of Med., Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care (Brian D. Smedley et al. eds., 2003) (arguing for a comprehensive strategy to address disparities in health care access). Agency for Healthcare Research & Quality, 2005 National Healthcare Disparities Report (2006), *available at* http://ahrq.gov/qual/nhdr05/fullreport/Index.htm.

309. *See generally* Norman Daniels, Just Health Care (1985) (arguing for distributive justice in health care); 1 President's Comm'n for the Study of EthicalProblems in Med. & Biomedical & Behavioral Research, Securing Access to Health Care: A Report on the Ethical Implications of Differences in the Availability of Health Services (1983) (concluding "that society has an ethical obligation to ensure equitable access to health care for all … [because of] the special importance of health care: its role in relieving suffering, preventing premature death, restoring functioning, increasing opportunity, providing information about an individual's condition, and giving evidence of mutual empathy and compassion), *available at* http://www.bioethics.gov/reports/past_commissions/securing_access.pdf.

310. Daniels Norman. The Functions of Insurance and the Fairness of Genetic Underwriting. In: Rothstein Mark A., editor. *Genetics and Life Insurance: Medical Underwriting and Social Policy.* 2004. p. 130. [Google Scholar]

311. Garner James M, et al. Medical Monitoring: The Evolution of a Cause of Action. *30 Envtl L Rep.* 2000;10024:10024. [Google Scholar]

312. *See generally* Maxwell J. Mehlman & Jeffrey R. Botkin, Access to the Genome: The Challenge to Equality (1998) (examining the issues surrounding how to distribute access to the new genetic technologies and discussing the social and ethical problems that these technologies pose).

313. *See, e.g.,* Fries James F, et al. Beyond Health Promotion: Reducing Need and Demand for Medical Care. *17 Health Aff.* 1998;70:70. [PubMed] [Google Scholar] (arguing that reducing the need and demand for medical services will result in better health for the individual and lower medical costs).

314. Edith Brown Weiss, In Fairness to Future Generations: International Law, Common Patrimony, and Intergenerational Equity 21 (1989).

315. Many of the philosophical writings on intergenerational equity rely or comment on the applicability of philosopher, John Rawls's works. Rawls argued that any generation's expectations and responsibilities should be evaluated by using a "veil of ignorance" as to its actual place in the sequence of generations. John Rawls, A Theory of Justice 136–37 (1971). *See also* Attfield Robin. Environmental Ethics and Intergenerational Equity. *41 Inquiry.* 1998;207:218. [Google Scholar].

316. Gardiner Stephen M. The Real Tragedy of the Commons. *30 Phil & Pub Aff.* 2002;387:402–03. [PubMed] [Google Scholar]. *See* Stephen M. Gardiner, *Protecting Future Generations: Intergenerational Buck-Passing, Theoretical Ineptitude and a Brief for a Global Core Precautionary Principle,* Handbook of Intergenerational Justice 148–69 (Joerg Chet Tremmel ed. 2006) (discussing the ethical and economic policy concerns surrounding intergenerational buck-passing).

317. *See* Kristin Shrader-Frechette, Environmental Justice: Creating Equality, Reclaiming Democracy 95–116 (Oxford Univ. Press 2002).

318. *See* Weiss, *supra* note 314, at 193–216.

319. *See* Page Edward. Intergenerational Justice and Climate Change. *47 Pol Stud.* 1999;53 [Google Scholar].

320. *See* Philip Kitcher, The Lives to Come: The Genetic Revolution and Human Possibilities 325 (1996).

321. *See* Weiss, *supra* note 314, at 217–55.

322. In theory, the effect of policy decisions on future generations is a concern of all government agencies and departments. In reality, the exigencies of the present often are given primacy over the remote interests of future generations. One innovative approach was adopted by the Israeli Knesset in 2001, when it created the Commission for Future Generations to protect the rights of future generations at the parliamentary level. *See* Shlomo Shoham & Nira Lamay, *Commission for Future Generations in the Knesset: Lessons Learnt*, *in* Handbook of Intergenerational Justice 244 (Joerg Chet Tremmel ed. 2006).

323. Weiss, *supra* note 314, at 38.

324. U. N. Educ., Scientific and Cultural Organization [UNESCO], *Universal Declaration on the Human Genome and Human Rights* 42 (1997), *available at* http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html (last visited Oct. 20, 2008).

325. Fraga et al., *supra* note 98, at 10609.

326. The built environment refers to the combination of physical conditions that affect humans, including their health. See generally Srivasan Shobha, O'Fallon Liam R, Dreary Allen. Creating Healthy Communities, Healthy Homes, Healthy People: Initiating a Research Agenda on the Built Environment and Public Health. *Am J Pub Health.* 2003;93:1446. [PMC free article] [PubMed] [Google Scholar]

327. C. S. Lewis, The Abolition of Man 36 (1947).

328. *See generally* Daniel J. Kevles, In the Name of Eugenics (1985) (explaining that Galton, an English scientist and pioneer of eugenics, intended eugenics to be a science of improving the human population by giving more suitable races orbloodlines a better chance of prevailing quickly over the less suitable).

329. *Id.* at 96–112.

330. *Id.* at 46–47.

331. *See generally* Robert Proctor, Racial Hygiene: Medicine under the Nazis (1988) (arguing that previous scholars underestimated the extent to which Nazi political initiatives arose from within the scientific community itself and the extent to which medical scientists actively designed and administered key elements of National Socialist racial policy).

332. *See generally* Allan Chase, The Legacy of Malthus: The Social Costs of the New Scientific Racism 135 (1977).

333. J. David Smith, The Eugenic Assault on America: Scenes in Red, White, and Black 6 (George Mason Univ. Press 1993).

334. Troy Duster, Backdoor to Eugenics (1990). *See also* Barbara Katz Rothman, The Tentative Pregnancy: Prenatal Diagnosis and the Future of Motherhood (1986) (discussing prenatal diagnosis and selective abortions offering new choices, while creating new structures and new limitations on choice).

335. Kitcher, *supra* note 320, at 196, 202.

336. Barbara Katz Rothman, Recreating Motherhood: Ideology and Technology in a Patriarchal Society 115–16 (1989).

337. *Id.* at 57–58.

338. Field Martha A. Killing "the Handicapped"–Before and After Birth. *16 Harv Women's LJ.* 1993;79:123–24. [PubMed] [Google Scholar]; Parens Erik, Asch Adrienne. The Disability Rights Critique of Prenatal Genetic Testing: Reflections and Recommendations. *29 Hastings Center Rep (Special Supp)* 1999;1 passim. [PubMed] [Google Scholar].

339. *See* Parens & Asch, *supra* note 338, at 2–3.

340. *See* Marteau Theresa M, Drake Harriet. Attributions for Disability: The Influence of Genetic Screening. *40 Soc Sci & Med.* 1994;1127:1130. [PubMed] [Google Scholar].

341. *See generally* Ted Peters, Playing God?: Genetic Determinism and Human Freedom (1997) (recognizing widespread discomfort with genetics predicated on the intent to alter human traits and concluding that moral considerations must guide genetic science).

342. Dobzhansky Theodosius. Man and Natural Selection. *49 Am Scientist.* 1961;285:296. [Google Scholar]

343. Allen Buchanan et al., From Chance to Choice: Genetics and Justice 60 (2000).

344. *See* Rothstein Mark A. Legal Conceptions of Equality in the Genomic Age. *25 L & Inequality.* 2007;429 [PMC free article] [PubMed] [Google Scholar] (discussing how "[t]he development of new methods of identifying individual genomic variation can either revolutionize societal conceptions of equality or add yet another basis for perpetuating inequality").