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

Mark A. Rothstein,[†] Yu Cai,^{††} and Gary E. Marchant^{†††}

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.

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

“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*.

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TABLE OF CONTENTS

- I. INTRODUCTION
- II. BACKGROUND
 - A. Description of Epigenetics
 - B. The Roles of Epigenetic Programming in Normal Cells
 - C. Examples of Abnormal Epigenetic Effects
 - 1. Cancer
 - 2. Adult Onset Diseases
 - 3. Transgenerational Effects of Endocrine Disrupting Chemicals
 - 4. Ionizing Radiation
 - 5. Smoking and Air Pollution
 - 6. Diet
 - 7. In Vitro Fertilization
 - 8. Aging
 - 9. Maternal Behavior
 - D. Unique Aspects of Epigenetic Changes
 - E. Questions Remaining to be Answered in Epigenetics Research
- III. LEGAL IMPLICATIONS
 - A. Regulatory Applications
 - 1. Environmental Regulation
 - 2. Food and Drug Regulation
 - 3. Occupational Safety and Health Regulation
 - B. Litigation Applications
 - C. Discrimination in Employment Against Fertile Women
 - D. Other Forms of Discrimination
- IV. ETHICAL IMPLICATIONS
 - A. Environmental Justice
 - B. Privacy and Confidentiality
 - C. Equitable Access to Health Care
 - D. Intergenerational Equity
 - E. Eugenics
- V. CONCLUSION

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 implica-

¹ Dana C. Dolinoy, Jennifer R. Weidman & Randy L. Jirtle, *Epigenetic Gene Regulation: Linking Early Developmental Environment to Adult Disease*, 23 REPRODUCTIVE TOXICOLOGY 297, 298 (2007).

² As one leading scientific journal recently observed, “[w]e have recently witnessed an explosion of research efforts, meetings and symposia, international initiatives, internet resources, commercial enterprises, and even a recent textbook dedicated to epigenetics.” Aaron D. Goldberg, C. David Allis & Emily Bernstein, *Epigenetics: A Landscape Takes Shape*, 128 CELL 635, 635 (2007). The National Institutes of Health selected epigenetics as one of its two top-priority “Roadmap Initiatives” for 2008 and has committed \$190 million in funding over the next five years. Elizabeth Pennisi, *Are Epigeneticists Ready for Big Science?*, 319 SCIENCE 1177 (2008).

tions 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

³ Conrad H. Waddington, *The Epigenotype*, 1 ENDEAVOUR 18, 18 (1942).

⁴ EPIGENETIC MECHANISMS OF GENE REGULATION 1 (Vincenzo E. A. Russo, Robert A. Martienssen & Arthur D. Riggs eds., 1996). DNA consists of a sequence of four different DNA bases or “nucleotides” that consist of adenine (A), thymine (T), guanine (G), and cytosine (C). The order of these nucleotides in a specific functional stretch of DNA called a gene conveys the informational content of DNA. In the DNA double helix, which consists of two parallel strands of DNA bound together in a coiled spiral, C’s always bind with G’s on the complementary strand, and A’s bind with T’s.

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

⁵ See BENJAMIN A. PIERCE, *GENETICS: A CONCEPTUAL APPROACH* 433-68 (2d ed. 2006) (explaining transcription and gene regulation, mutation and gene products).

⁶ Wolf Reik, *Stability and Flexibility of Epigenetic Gene Regulation in Mammalian Development*, 447 *NATURE* 425, 425 (2007).

⁷ Methylation of cytosine (C) nucleotide bases may only occur where the C is followed by a guanine (G) base, in what is called a CpG dinucleotide in vertebrates. Methylation of C also occurs to CpNG sites in some organisms. Adrian Bird, *DNA Methylation Patterns and Epigenetic Memory*, 16 *GENES & DEV.* 6, 9 (2002).

⁸ The “p” refers to the phosphorous group that helps bind together adjacent base pairs in the DNA sequence.

⁹ Romulo M. Brena & Joseph F. Costello, *Genome-Epigenome Interactions in Cancer*, 16 *HUM. MOLECULAR GENETICS* R96, R96 (2007); Andrew P. Feinberg & Benjamin Tycko, *The History of Cancer Epigenetics*, 4 *NATURE REV. GENETICS* 143, 143 (2004); DNA methylation of CG dinucleotides is one of the mechanisms of epigenetic regulation. William Coleman & Ashley Riverbark, *Quantitative DNA Methylation Analysis: the Promise of High-Throughput Epigenomic Diagnostic Testing in Human Neoplastic Disease*, 8 *J. MOLECULAR DIAGNOSTICS* 152, 153-4 (2006) (70-80% of the CGs in the entire genome are methylated to maintain chromosomal stability. The remaining 20-30% of CGs are clustered, many of which are associated with genes).

¹⁰ See Jessica E. Sutherland & Max Costa, *Epigenetics and the Environment*, 983 *ANNALS N.Y. ACAD. SCI.* 151, 152 (2003).

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

¹¹ Rebecca E. Watson & Jay I. Goodman, *Epigenetics and DNA Methylation Come of Age in Toxicology*, 67 TOXICOL. SCIENCES 11, 11-12 (2002).

¹² Brena & Costello, *supra* note 9, at R96; Feinberg & Tycko, *supra* note 9, at 146.

¹³ Adrian Bird, *Perceptions of Epigenetics*, 447 NATURE 396, 397 (2007). Acetylation is chemically adding an acetyl group (CH₃-CO-) to the histone protein.

¹⁴ Moshe Szyf, *The Dynamic Epigenome and its Implications in Toxicology*, 100 J. TOXICOLOGICAL SCI. 7, 9 (2007). Deacetylation is removing an acetyl group (CH₃-CO-) from the histone protein.

¹⁵ See generally Christopher B. Schaefer et al., *Epigenetic Decisions in Mammalian Germ Cells*, 316 SCIENCE 398, 398 (2007) (stating that RNA dependant DNA methylation is a candidate mechanism for *de novo* DNA methylation).

¹⁶ Goldberg et al., *supra* note 2, at 637.

¹⁷ Paula M. Vertino et al., *DNMT1 is a Component of a Multiprotein 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,

Replication Complex, 1 CELL CYCLE 416, 416 (2002). Unlike DNA methylation changes, which are heritable, no evidence or known mechanism exist for transgenerational replication of other epigenetic changes, such as histone modifications. Mark Ptashne, *On the Use of the Word 'Epigenetic,'* 17 CURRENT BIOLOGY R233, R233 (2007).

¹⁸ Catherine Gallou-Kabani et al., *Nutri-epigenomics: Lifelong Remodelling of our Epigenomes by Nutritional and Metabolic Factors and Beyond*, 45 CLINICAL CHEMISTRY & LABORATORY MED. 321, 321, 323 (2007).

¹⁹ See Jennifer Brennan & Blanche Capel, *One Tissue, Two Fates: Molecular Genetic Events that Underlie Testis Versus Ovary Development*, 5 NATURE REV. GENETICS 509, 510 (2004) (the stage of sex determination starts during the seventh week of pregnancy, when the differentiation of the single primordial-gonad to a testis or an ovary determines the sex of the embryo); Dolinoy et al., *supra* note 1, at 298 (“[The human] epigenome is particularly susceptible to deregulation during gestation, neonatal development, puberty, and old age.”); Philip Robichaud, *Metaphysics and Morality at the Boundaries of Life*, 31 J. MED. & PHIL. 97, 100-102 (2006) (analyzing theories that argue that the two most critical stages of epigenetic programming in human embryonic development are gastrulation and sex determination, gastrulation takes place around 16 days after fertilization in humans, during which cell migration restructures drastically the embryo morphology).

²⁰ Dolinoy et al., *supra* note 1, at 298.

²¹ *Id.* at 300; Szyf, *supra* note 14, at 9.

²² Red blood cells are an exception because these cells lack a nucleus, and thus lack most of their genetic material. In all other types of cells, spontaneous muta-

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

tions may arise in individual cells during cell replication.

²³ Andrew P. Feinberg, *Phenotypic Plasticity and the Epigenetics of Human Disease*, 447 NATURE 433, 437 (2007).

²⁴ R. Keith Slotkin & Robert Martienssen, *Transposable Elements and the Epigenetic Regulation of the Genome*, 8 NATURE REV. GENETICS 272, 272 (2007).

²⁵ See Timothy H. Bestor, *Cytosine Methylation Mediates Sexual Conflict*, 19 TRENDS GENETICS 185, 185 (2003); Robert A. Waterland & Randy L. Jirtle, *Early Nutrition, Epigenetic Changes at Transposons and Imprinted Genes, and Enhanced Susceptibility to Adult Chronic Diseases*, 20 NUTRITION 63, 65 (2004).

²⁶ Randy L. Jirtle & Michael K. Skinner, *Environmental Epigenomics and Disease Susceptibility*, 8 NATURE REV. GENETICS 253, 253 (2007); see, Slotkin & Martienssen, *supra* note 24, at 272 (“[T]he genome has evolved epigenetic ‘defense’ mechanisms to suppress [transposable elements] activity.”).

²⁷ See sources cited *supra* notes 20-21.

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 addition 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 post-natally, 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

²⁸ Zdenko Herceg & Pierre Hainaut, *Genetic and Epigenetic Alterations as Biomarkers for Cancer Detection, Diagnosis and Prognosis*, 1 MOLECULAR ONCOLOGY 26, 34 (2007); Jirtle & Skinner, *supra* note 26, at 255; Randy L. Jirtle & Jennifer R. Weidman, *Imprinted and More Equal*, 95 AM. SCIENTIST 143, 143, 145 (2007).

²⁹ Jirtle & Skinner, *supra* note 26, at 255; See Jon F. Wilkins & David Haig, *What Good is Genomic Imprinting: The Function of Parent-Specific Gene Expression*, 4 NATURE REV. GENETICS 359 (2003).

³⁰ Jirtle & Skinner, *supra* note 26, at 256.

³¹ Jirtle & Weidman, *supra* note 28, at 149.

³² A long-known example of such parent-of-origin phenomena, which only recently was realized to operate by an epigenetic mechanism, is the different effect of crossing a female horse with a male donkey to produce a mule, whereas a male horse and female donkey will produce a "hinny." Philip Hunter, *The Silence of the Genes: Is Genomic Imprinting the Software of Evolution or Just a Battleground for Gender Conflict?*, 8 EMBO REP. 441, 441 (2007).

³³ Alexander Gimelbrant et al., *Widespread Monoallelic Expression on Human Autosomes*, 318 SCIENCE 1136, 1136-40 (2007).

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

³⁴ Peter D. Gluckman et al., *Metabolic Plasticity During Mammalian Development is Directionally Dependent on Early Nutritional Status*, 104. PROC. NAT'L ACAD. SCI. 12796, 12796 (2007).

³⁵ Jirtle & Skinner, *supra* note 26, at 253.

³⁶ Rachael Moeller Gorman, *The New Heredity*, PROTOMAG, Fall 2007, at 39, 39, available at http://protomag.com/issues/2007_fall/pdfs/heredity.pdf.

³⁷ Reinhard Stöger, *The Thrifty Epigenotype: An Acquired and Heritable Predisposition for Obesity and Diabetes?*, 30 BIOESSAYS 156, 159-60 (2008).

³⁸ Leslie A. Pray, *Epigenetics: Genome, Meet Your Environment*, SCIENTIST, July 5, 2004, at 14, 14 (quoting Randy Jirtle).

³⁹ See RICHARD W. BURKHARDT, JR., *THE SPIRIT OF SYSTEM: LAMARCK AND EVOLUTIONARY BIOLOGY* 1-2 (1977).

⁴⁰ See Stöger, *supra* note 37, at 159.

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

⁴¹ Matthew D. Anway et al., *Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility*, 308 SCI. 1466, 1466 (2005); Marcus E. Pembrey et al., *Sex-Specific, Male-Line Transgenerational Responses in Humans*, 14 EUR. J. HUM. GENETICS 159, 159–66 (2006) (demonstrating that an inherited disease phenotype in humans that is potentially induced by an epigenetic phenomenon).

⁴² Dolinoy et al., *supra* note 1, at 298; Anway et al., *supra* note 41, at 1466.

⁴³ Andrew P. Feinberg, *Epigenetics at the Epicenter of Modern Medicine*, 299 JAMA 1345, 1348 (2008).

⁴⁴ Peter A. Jones & Stephen B. Baylin, *The Epigenomics of Cancer*, 128 CELL 683 *passim* (2007).

⁴⁵ Szyf, *supra* note 14, at 15.

⁴⁶ Stephen B. Baylin et al., *Alterations in DNA Methylation: A Fundamental Aspect of Neoplasia*, 72 ADVANCES CANCER RES. 141, 155 (1998); Herceg & Hainaut, *supra* note 28, at 32–33.

⁴⁷ Feinberg & Tycko, *supra* note 9, at 143; Manel Esteller, *Molecular Origins of Cancer: Epigenetics in Cancer*, 358 NEW ENG. J. MED. 1148, 1149–50 (2008).

⁴⁸ Feinberg & Tycko, *supra* note 9, at 143.

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

⁴⁹ Esteller, *supra* note 47, at 1149.

⁵⁰ Sutherland & Costa, *supra* note 10, at 152.

⁵¹ Andrew P. Feinberg, *Genomic Imprinting and Gene Activation in Cancer*, 4 NATURE GENETICS 110, 113 (1993).

⁵² *Id.* at 112.

⁵³ Beckwith–Wiedemann syndrome, or BWS, is a rare overgrowth genetic or epigenetic syndrome associated with an increased risk of embryonic tumor formation, which leads to a 20% mortality rate among newborns with BWS. See ROBBINS & COTRAN, *PATHOLOGIC BASIS OF DISEASES* 505 (Vinay Kumar, Abul Abbas, & Nelson Fausto eds., Elsevier Saunders, 7th ed. 2003).

⁵⁴ Michael R. DeBaun & Andrew P. Feinberg, *IGF2, H19, p57^{KIP2}, and LIT1 and the Beckwith–Wiedemann Syndrome*, in *INBORN ERRORS OF DEVELOPMENT: THE MOLECULAR BASIS OF CLINICAL DISORDERS OF MORPHOGENESIS* 758, 758–65 (Charles J. Epstein et al. eds., 2004).

⁵⁵ See Matthew D. Anway & Michael K. Skinner, *Epigenetic Transgenerational Actions of Endocrine Disruptors*, 147 *ENDOCRINOLOGY* S43, S43 (2007)

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

(defects in the epigenome changes during these critical stages of embryonic development are known to lead to aberrant gene expression and diseases such as cancer); Feinberg, *supra* note 23, at 438.

⁵⁶ Dolinoy et al. *supra* note 1, at 298.

⁵⁷ Jirtle & Skinner, *supra* note 26, at 253-54.

⁵⁸ Jonathan Mill et al., *Epigenomic Profiling Reveals DNA-Methylation Changes Associated with Major Psychosis*, 82 AM. J. HUM. GENETICS 696, 697 (2008).

⁵⁹ *Id.*

⁶⁰ Angelman Syndrome (AS), is a neurological genetic disorder due to the abnormal imprinting on the maternal copy of chromosome 15. AS is associated with developmental delay and mental retardation. See Raymond J. Barry et al., *Behavioral Aspects of Angelman Syndrome: A Case Control Study*, 132A AM. J. MED. GENETICS 8, 8-9 (2005).

⁶¹ See Suzanne B. Cassidy et al., *Prader-Willi and Angelman Syndromes: Sister Imprinted Disorders*, 97 AM. J. MED. GENETICS 136, 136-37 (2000) (Prader-Willi syndrome (PWS) is a complex disorder caused by the abnormal imprinting on the paternal derived chromosome and has fifteen distinct characteristics in comparison to Angelman Syndrome.).

⁶² Myriam Fornage, *Unraveling Hypertension: Epigenomics Comes of Age*, 8 PHARMACOGENOMICS 125, 125 (2007); Rachel L. Miller & Shuk-mei Ho, *Environmental Epigenetics and Asthma: Current Concepts and Call for Studies*, 177 AM. J. RESPIRATORY & CRITICAL CARE MED. 567, 567 (2008).

⁶³ See, e.g., Stöger, *supra* note 37, at 159-62; Waterland & Jirtle, *supra* note 25, at 63.

conditions 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

⁶⁴ See Stöger, *supra* note 37, at 160.

⁶⁵ Gian-Paolo Ravelli, Zena A. Stein & Mervyn W. Susser, *Obesity in Young Men After Famine Exposure in Utero and Early Infancy*, 295 NEW ENG. J. MED. 349, 349-52 (1976).

⁶⁶ Ruthann M. Giusti, Kumiko Iwamoto & Elizabeth E. Hatch, *Diethylstilbestrol Revisited: A Review of the Long-Term Health Effects*, 122 ANNALS INTERNAL MED. 778, 778-88 (1995); June Machover Reinisch, Mary Ziembra-Davis, & Stephanie A. Sanders, *Hormonal Contributions to Sexually Dimorphic Behavioral Development in Humans*, 16 PSYCHONEUROENDOCRINOLOGY 213, 213-78 (1991).

⁶⁷ M.M. Brouwers et al., *Hypospadias: A Transgenerational Effect of Diethylstilbestrol?*, 21 HUM. REPROD. 666, 666-69 (2006); Retha R. Newbold, Elizabeth Padilla-Banks & Wendy N. Jefferson, *Adverse Effects of the Model Environmental Estrogen Diethylstilbestrol Are Transmitted to Subsequent Generations*, 147 ENDOCRINOLOGY (SUPP.) 11, 15-16 (2006).

⁶⁸ Anway et al., *supra* note 41, at 1467; Jirtle & Skinner, *supra* note 26, at 257-58.

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 transgenerational 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

⁶⁹ Jirtle & Skinner, *supra* note 26, at 257-58.

⁷⁰ Julianne Byrne et al., *Genetic Disease in Offspring of Long-Term Survivors of Childhood and Adolescent Cancer*, 62 AM. J. HUM. GENETICS 45, 45-52 (1998).

⁷¹ Ruth Barber, et al., *Elevated Mutation Rates in the Germ Line of First- and Second-generation Offspring of Irradiated Male Mice*, 99 PROC. NAT'L ACAD. SCI. U.S. 6877, 6877 (2002).

⁷² Igor Koturbash et al., *Epigenetic Dysregulation Underlies Radiation-induced Transgenerational Genome Instability in Vivo*, 66 INT'L J. RADIATION ONCOLOGY BIOLOGY PHYSICS 327, 327-30 (2006).

⁷³ *Id.* at 330.

⁷⁴ Pembrey et al., *supra* note 41.

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 B₁₂, 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

⁷⁵ *Id.*

⁷⁶ *Id.*

⁷⁷ Yu-Fen Li et al., *Maternal and Grandmaternal Smoking Patterns Are Associated with Early Childhood Asthma*, 127 CHEST 1232, 1238 (2005).

⁷⁸ Jinming Liu et al., *Combined Inhaled Diesel Exhaust Particles and Allergen Exposure Alter Methylation of T Helper Genes and IgE Production In Vivo*, 102 TOXICOLOGICAL SCI. 76, 80 (2008).

⁷⁹ Sharon A. Ross, *Diet and DNA Methylation Interactions in Cancer Prevention*, 983 ANN. N.Y. ACAD. SCI. 197, 202-204 (2003) (“Epimediological, preclinical, and clinical evidence suggest that diet is a significant factor in cancer prevention and cancer risk.”).

⁸⁰ Robert A. Waterland et al., *Maternal Methyl Supplements Increase Offspring DNA Methylation at Axin Fused*, 44 GENESIS 401, 403 (2006).

⁸¹ Jirtle & Skinner, *supra* note 26, at 255.

⁸² Lionel A. Poirier, *The Role of Methionine in Carcinogenesis in vivo*, in 206 ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY 269, 269-82 (Lionel A. Poirier et al. eds., 1986).

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 B₁₂) 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

⁸³ Kevin D. Sinclair et al., *DNA Methylation, Insulin Resistance, and Blood Pressure in Offspring Determined by Maternal Periconceptual B Vitamin and Methionine Status*, 104 PROC. NAT'L ACAD. SCI. 19351 (2007).

⁸⁴ Sang-Woon Choi et al., *Chronic Alcohol Consumption Induces Genomic but not p53-Specific DNA Hypomethylation in Rat Colon*, 129 J. NUTRITION 1945, 1945-50 (1999).

⁸⁵ See Dana C. Dolinoy, Jennifer R. Weidman, Robert A. Waterland & Randy L. Jirtle, *Maternal Genistein Alters Coat Color and Protects A^{vy} Mouse Offspring From Obesity by Modifying the Fetal Epigenome*, 114 ENVTL. HEALTH PERSP. 567, 571 (2006).

⁸⁶ Jennifer E. Cropley et al., *Germ-line Epigenetic Modification of the Murine A^{vy} Allele by Nutritional Supplementation*, 103 PROC. NAT'L ACAD. SCI. 17, 308 (2006).

⁸⁷ Craig A. Cooney, *Germ Cells Carry the Epigenetic Benefits of Grandmother's Diet*, 103 PROC. NAT'L ACAD. SCI. 17071, 17071-72 (2006).

⁸⁸ Gunnar Kaati et al., *Transgenerational Response to Nutrition, Early Life Circumstances and Longevity*, 15 EUR. J. HUM. GENETICS 784, 784, 786 (2007).

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

⁸⁹ Thomas M. Price, Susan K. Murphy & Edward V. Younglai, *Perspectives: The Possible Influence of Assisted Reproductive Technologies on Transgenerational Reproductive Effects of Environmental Endocrine Disruptors*, 96 TOXICOLOGICAL SCI. 218, 218 (2007).

⁹⁰ *Id.* at 223.

⁹¹ *Id.*

⁹² DeBaun & Feinberg, *supra* note 54. *But see* Sarah Bowdin et al., *A Survey of Assisted Reproductive Technology Births and Imprinting Disorders*, 22 HUM. REPROD. 3237 (2007) (finding a much smaller increase in these conditions in children born after *in vitro* fertilization than previously reported).

⁹³ Cf. Angela Sparago et al., *Mechanisms Causing Imprinting Defects in Familial Beckwith-Wiedemann Syndrome with Wilms' Tumor*, 16 HUMAN MOLECULAR GENETICS 254, 255 (2007) (showing that Familial Beckwith-Wiedemann Syndrome is characterized by dominant maternal transmission, loss of imprinting, and predisposition to tumors).

⁹⁴ See Maëlle Pannetier & Robert Feil, *Epigenetic Stability of Embryonic Stem Cells and Developmental Potential*, 25 TRENDS BIOTECHNOLOGY 556, 560 (2007).

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, includ-

⁹⁵ CENTER FOR VETERINARY MED., U.S. FOOD AND DRUG ADMIN., ANIMAL CLONING: A RISK ASSESSMENT 8 (2008), available at http://www.fda.gov/cvm/Documents/CloningRiskAssessment_FINAL.pdf.

⁹⁶ C. Fuke et al., *Age Related Changes in 5-methylcytosine Content in Human Peripheral Leukocytes and Placentas: An HPLC-Based Study*, 68 ANNALS HUM. GENETICS 196, 198-99 (2004).

⁹⁷ Johannes Gräff & Isabelle M. Mansuy, *Epigenetic Codes in Cognition and Behavior*, 192 BEHAVIOURAL BRAIN RES. 70, 76-77 (2008).

⁹⁸ Mario F. Fraga et al., *Epigenetic Differences Arise During the Lifetime of Monozygotic Twins*, 102 PROC. NAT'L. ACAD. SCIENCES 10604, 10609 (2005); Emile Zuckerkandl & Giacomo Cavalli, *Combinatorial Epigenetics, "Junk DNA," and the Evolution of Complex Organisms*, 390 GENE 232, 239 (2007) (noting that the observation of acquired epigenetic differences “attracts attention to an important potential implication of the inferred genetic/epigenetic partnership, namely, that it likely has a Lamarckian dimension”).

⁹⁹ Liang Liu et al., *Aging, Cancer and Nutrition: The DNA Methylation Connection*, 124 MECHANISMS AGEING & DEV. 989, 992 (2003); Fraga et al., *supra* note 98, at 10609.

ing 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

¹⁰⁰ Q. Lu et al., *Epigenetics, Disease, and Therapeutic Interventions*, 5 AGEING RES. REV. 449, 451 (2006).

¹⁰¹ Ian C.G. Weaver et al., *Epigenetic Programming by Maternal Behavior*, 7 NATURE NEUROSCIENCE 847, 847 (2004).

¹⁰² *Id.* at 850; Ian C.G. Weaver et al., *Reversal of Maternal Programming of Stress Responses in Adult Offspring Through Methyl Supplementation: Altering Epigenetic Marking Later in Life*, 25 J. NEUROSCIENCE 11045 (2005).

¹⁰³ Weaver et al., *supra* note 101; Ian C.G. Weaver, M.J. Meaney & Moshe Szyf, *Maternal Care Effects on the Hippocampal Transcriptome and Anxiety-Mediated Behaviors in the Offspring that are Reversible in Adulthood*, 103 PROC. NAT’L ACAD. SCI. 3480 (2006).

¹⁰⁴ Jirtle & Skinner, *supra* note 26, at 259.

¹⁰⁵ Anita L. Kozyrskyj et al., *Continued Exposure to Maternal Distress in Early Life Is Associated with an Increased Risk of Childhood Asthma*, 177 AM. J. RESPIRATORY & CRITICAL CARE MED. 142, 143 (2008).

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

¹⁰⁶ Jones & Baylin, *supra* note 44, at 683.

¹⁰⁷ Jirtle & Skinner, *supra* note 26, at 258.

¹⁰⁸ See Oliver J. Rando & Kevin J. Verstrepen, *Timescales of Genetic and Epigenetic Inheritance*, 128 CELL 655, 655-61 (2007).

¹⁰⁹ Dolinoy et al., *supra* note 1, at 298.

¹¹⁰ Feinberg, *supra* note 43, at 1346.

¹¹¹ Dolinoy et al., *supra* note 1, at 298.

¹¹² Herceg & Hainaut, *supra* note 28, at 36; Szyf, *supra* note 14, at 19.

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

¹¹³ Stella Marie Reamon-Buettner & Jürgen Borlak, *A New Paradigm in Toxicology and Teratology: Altering Gene Activity in the Absence of DNA Sequence Variation*, 24 REPROD. TOXICOLOGY 20, 27 (2007).

¹¹⁴ Szyf, *supra* note 14, at 13-14.

¹¹⁵ *Id.* at 8.

¹¹⁶ Jirtle & Skinner, *supra* note 26, at 256.

¹¹⁷ Szyf, *supra* note 14, at 10.

¹¹⁸ Huidong Shi, Michael X. Wang, & Charles W. Caldwell, *CpG Islands: Their Potential as Biomarkers for Cancer*, 7(5) EXPERT REV. MOLECULAR DIAGNOSIS 519, 520 (2007).

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

¹¹⁹ See generally, Lanlan Shen et al., *Integrated Genetic and Epigenetic Analysis Identifies Three Different Subclasses of Colon Cancer*, 104 PROC. NAT'L ACAD. SCI. 18654, 18654 (2007) ("[C]ertain individuals appear predisposed to aberrant... hypermethylation ...at several tumor suppressor genes."); See Sparago et al., *supra* note 93. The penetrance of these mutations is found correlated with the hypermethylation of the mutant allele that causes BWS. In the study of colon cancer, it is observed that some individuals appear predisposed to aberrant hypermethylation at several tumor suppressor genes.

¹²⁰ See William B. Coleman & Ashley G. Riverbark, *Quantitative DNA Methylation Analysis: the Promise of High-Throughput Epigenomic Diagnostic Testing in Human Neoplastic Disease*, 8 J. MOLECULAR DIAGNOSTICS 152, 155-6 (2006).

¹²¹ Shi et al., *supra* note 118, at 526.

¹²² *Id.* at 520; see also, Aggerholm Anni, et al., *Promoter Hypermethylation of p15^{INK4B}, HIC1, CDH1, and ER is Frequent in Myelodysplastic Syndrome and Predicts Poor Prognosis in Early-stage Patients*, 76(1) EUR. J. HAEMATOLOGY 23, 28 (2005).

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

¹²³ Jirtle & Skinner, *supra* note 26, at 259.

¹²⁴ Dolinoy et al., *supra* note 1, at 303; Watson & Goodman, *supra* note 11, at 12.

¹²⁵ See *supra* notes 66-69 and accompanying text.

¹²⁶ Sutherland & Costa, *supra* note 10, at 153-55.

¹²⁷ Masufumi Takiguchi et al., *Effects of Cadmium on DNA-(Cytosine-5) Methyltransferase Activity and DNA Methylation Status during Cadmium-Induced Cellular Transformation*, 286 EXPERIMENTAL CELL RES. 355 (2003).

¹²⁸ R.S. Okoji et al., *Sodium Arsenite Administration via Drinking Water Increases Genome-Wide and Ha-ras DNA Hypomethylation in Methyl-Deficient C57BL/6J Mice*, 23 CARCINOGENESIS 777, 777-85 (2002).

¹²⁹ Dana C. Dolinoy, Dale Huang & Randy L. Jirtle, *Maternal Nutrient Supplementation Counteracts Bisphenol A-Induced DNA Hypomethylation in Early Development*, 104 PROC. NAT'L ACAD. SCI. 13056, 13056 (2007); Shuk-Mei Ho et al., *Developmental Exposure to Estradiol and Bisphenol A Increases Susceptibility to Prostate Carcinogenesis and Epigenetically Regulates Phosphodiesterase Type 4 Variant 4*, 66 CANCER RES. 5624, 5624-32 (2006).

¹³⁰ 42 U.S.C. §§ 7401-7671q (2000).

¹³¹ 33 U.S.C. §§ 1251-1387 (2000).

¹³² 15 U.S.C. §§ 2601-2629 (2000).

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:

¹³³ 42 U.S.C. §§ 9601-9675 (2000).

¹³⁴ 42 U.S.C. §§ 6901-6992k (2000).

¹³⁵ 42 U.S.C. §§ 300f-300j-25 (2000).

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.).

¹³⁸ U.S. ENVTL. PROTECTION AGENCY, PESTICIDES: REGULATING PESTICIDES, <http://www.epa.gov/pesticides/regulating/index.htm> (last visited Oct. 28, 2008).

¹³⁹ 21 U.S.C. § 346a(p).

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

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 transgenerational 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

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.

¹⁴⁵ Watson & Goodman, *supra* note 11, at 14.

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.

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

¹⁴⁷ Dolinoy et al., *supra* note 129, at 13059.

¹⁴⁸ Carol J. Henry et al., *Use of Genomics in Toxicology and Epidemiology: Findings and Recommendations of a Workshop*, 110 ENVTL. HEALTH .PERSP. 1047, 1049 (2002); COMM. ON APPLICATIONS OF TOXICOGENOMIC TECHNOLOGIES TO PREDICTIVE TOXICOLOGY, NAT’L RESEARCH COUNCIL, APPLICATIONS OF TOXICOGENOMIC TECHNOLOGIES TO PREDICTIVE TOXICOLOGY AND RISK ASSESSMENT 187 (2007).

¹⁴⁹ Dolinoy et al., *supra* note 85, at 567.

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. Kristina A. Thayer & Paul M. Foster, *Workgroup Report: National Toxicology Program Workshop on Hormonally Induced Reproductive Tumors – Relevance of Rodent Bioassays*, 115 ENVTL. HEALTH PERSP. 1351, 1355 (2007).

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

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 miti-

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.

gate 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. Jekyll 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

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 Gerda Egger et al., *Epigenetics in Human Disease and Prospects for Epigenetic Therapy*, 429 NATURE 457, 460 (2004); Jeneen Interlandi, *Chemo Control, : Drugs Target Epigenetic Changes in Cancer Cells*, SCI. AM., April 2007, at 24, 24; 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 Andrew P. Feinberg, *An Epigenetic Approach to Cancer Etiology*, 13 CANCER J. 70, 73 (2007).

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

¹⁶⁴ *Id.*

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

¹⁶⁶ Szyf, *supra* note 14, at 8.

¹⁶⁷ Susan H. Wei, Robert Brown & Tim H.M Huang, *Aberrant DNA Methylation in Ovarian Cancer: Is There an Epigenetic Predisposition to Drug Response?*, 983 ANN. N.Y. ACAD. SCI. 243, 244 (2003).

¹⁶⁸ Szyf, *supra* note 14, at 8.

¹⁶⁹ *Id.* at 17.

¹⁷⁰ *Id.* at 8, 17.

¹⁷¹ Mukesh Verma & Upender Manne, *Genetic and Epigenetic Biomarkers in Cancer Diagnosis and Identifying High Risk Populations*, 60 CRITICAL REV. ONCOLOGY/HEMATOLOGY 9, 13 (2006).

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

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 Einav Nili Gal-Yam et al., *Cancer Epigenetics: Modifications, Screening and Therapy*, 59 ANN. REV. MED. 267, 274 (2008); 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 Oncology 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).

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

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).

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 citation¹⁹⁰ and assessing a range of civil and criminal penalties¹⁹¹ 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:

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).

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 Petroleum Institute*,¹⁹⁸ the plurality opinion stated that “the statute was not designed to require employers to provide absolutely risk-free workplaces when-

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).

ever 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

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 Roger Clegg, Bragdon v. Abbott, *Asymptomatic Genetic Conditions, and Antidiscrimination Law: A Conservative Approach*, 3 J. HEALTH CARE L. & POL’Y 409 (2000), Mark .S. Dichter & Sarah E. Sutor, *The New Genetic Age: Do Our Genes Make Us Disabled Individuals Under the Americans with Disabilities Act?*, 42 VILL. L. REV. 613 (1997), and Richard A. Epstein, *The Legal Regulation of Genetic Discrimination: Old Responses to New Technology*, 74 B.U. L. REV. 1 (1994) (supporting the use of genetic testing), with Henry T. Greely, *Genotype Discrimination: The Complex Case for Some Legislative Protection*, 149 U. PA. L. REV. 1483 (2001) (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 Paul W. Brandt-Rauf & Sherry I. Brandt-Rauf, *Genetic Testing in the Workplace: Ethical, Legal, and Social Implications*, 25 ANN. REV. PUB. HEALTH 139, 141 (2004); Robert J. McCunney, *Genetic Testing: Ethical Implications in the Workplace*, 17 OCCUP. MED. 665, 668-69 (2002).

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 Nondiscrimination 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

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).

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

²⁰⁸ Kaimipono David Wenger, *Causation and Attenuation in the Slavery Reparations Debate*, 40 U.S.F. L. REV. 279, 314 (2006).

²⁰⁹ Tracey I. Batt, *DES Third-Generation Liability: A Proximate Cause*, 18 CARDOZO L. REV. 1217, 1223-29 (1996) (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).

*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

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.

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

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.

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

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*, *supra* note 209, at 1242.

²³⁴ *Id.*

²³⁵ *Id.*

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 flood-gates 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.

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

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

²³⁸ John B. Maynard, *Third-Generation-DES Claims*, 27 NEW ENG. L. REV. 241, 285 (1992).

²³⁹ Feinberg, *supra* note 23, 438.

²⁴⁰ Arturas Petronis, *Epigenetics and Twins: Three Variations on the Theme*, 22 TRENDS GENETICS 347, 348 (2006).

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 workplace 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

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 Rosenstock et al. eds. 2005).

²⁴⁶ *Id.*

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

²⁴⁷ See Laura S. Welch, *Decisionmaking About Reproductive Hazards*, 1 SEM. OCCUP. MED. 97, 105 (1986).

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.*

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 protective 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

²⁵⁶ Deborah Rice & Stan Barone, Jr., *Critical Periods of Vulnerability for the Developing Nervous System: Evidence from Humans and Animal Models*, 108 ENVTL. HEALTH PERSP. (SUPP. 3) 511 *passim* (2000).

²⁵⁷ See David J.P. Barker, *Fetal Programming of Coronary Heart Disease* 13 TRENDS IN ENDOCRINOLOGY & METABOLISM 364, 364 (2002).

²⁵⁸ See Hugh A. Barton et al., *Assessing Susceptibility from Early-Life Exposure to Carcinogens*, 113 ENVTL. HEALTH PERSP. 1125, 1125 (2005); see also Jennifer D. Cook et al., *Interaction Between Genetic Susceptibility and Early-Life Environmental Exposure Determines Tumor-Suppressor-Gene Penetrance*, 102 PROC. NAT'L ACAD. SCI. 8644 (2005).

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).

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 section²⁶⁴ 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

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 Mark A. Rothstein, *Putting the Genetic Information Nondiscrimination Act in Context*, 10 GENETICS IN MED. 655 (2008).

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

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

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 Mark A. Rothstein & Meghan K. Talbott, *Compelled Disclosure of Health Information: Protecting Against the Greatest Potential Threat to Privacy*, 295 JAMA 2882, 2882 (2006). Furthermore, it is difficult to justify affording special treatment to genetic or epigenetic information than other predictive health information. See Mark A. Rothstein, *Genetic Exceptionalism and Legislative Pragmatism*, HASTINGS CENTER REP., July-Aug. 2005, at 27, 31-32.

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

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

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 Cathleen D. Zick et al., *Genetic Testing for Alzheimer's Disease and its Impact on Insurance Purchasing Behavior*, 24 HEALTH AFFAIRS 483, 483 (2005) (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

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

and loss of social cohesion are likely to affect health).

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

²⁸⁰ See Robert W. Williams, *Environmental Injustice in America and Its Politics of Scale*, 18 POL. GEOG. 49-73 (1999) (discussing politics of environmental justice).

²⁸¹ Clifford Rechtschaffen, *Advancing Environmental Justice Norms*, 37 U.C. DAVIS L. REV. 95, 96 (2003). 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 SCHLOSSBERG, *DEFINING ENVIRONMENTAL JUSTICE: THEORIES, MOVEMENTS, AND NATURE* (Oxford Univ. Press 2007) (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. Gerald Torres, *Environmental Justice: The Legal Meaning of a Social Movement*, 15 J.L. & COM. 597, 603 (1996).

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).

justice lack empirical foundations²⁸⁵ 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 ethnic-

²⁸⁵ William Bowen, *An Analytical Review of Environmental Justice Research: What Do We Really Know?*, 29 ENVTL. MGMT. 3 (2002).

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* Manuel Pastor, Jr., Jim Sadd & John Hipp, *Which Came First? Toxic Facilities, Minority Move-in, and Environmental Justice*, 23 J. URB. AFF. 1, 1-21 (2001) (finding that minorities attract toxic storage and disposal facilities).

²⁸⁷ Tseming Yang, *Melding Civil Rights and Environmentalism: Finding Environmental Justice's Place in Environmental Regulation*, 26 HARV. ENVTL. L. REV. 1, 4-8 (2002).

²⁸⁸ ENVTL. PROTECTION AGENCY, OFFICE OF POLICY PLANNING AND EVALUATION, ENVIRONMENTAL EQUITY: REDUCING RISK FOR ALL COMMUNITIES, 12 (1992). *See* Eric K. Yamamoto & Jen-L W. Lyman, *Racializing Environmental Justice*, 72 U. COLO. L. REV. 311, 318 (2001).

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).

ity, 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

²⁹¹ See Gary E. Marchant & Jamie A. Grodsky, *Genomics and Environmental Justice: Some Preliminary Thoughts*, GENOMICS AND ENVIRONMENTAL REGULATION (Richard R. Sharp, Gary E. Marchant & Jamie A. Grodsky eds. 2008) (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 Luz Claudio, *Standing on Principle: The Global Push for Environmental Justice*, 115 ENVTL. HEALTH PERSP. A 501 (2007) (summarizing the environmental justice movement).

²⁹⁴ Torres, *supra* note 281, at 617.

²⁹⁵ See, e.g., Charles Lee, *Environmental Justice: Building a Unified Vision of Health and the Environment*, 110 ENVTL. HEALTH PERSP. (SUPP. 2) 141 (2002).

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?

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); R. Andorno, *The Right Not to Know: An Autonomy Based Approach*, 30 J. MED. ETHICS 435, 435-36 (2004).

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).

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

³⁰¹ See, e.g., GENETIC SECRETS: PROTECTING PRIVACY AND CONFIDENTIALITY IN THE GENETIC ERA (Mark A. Rothstein ed., 1997); Mark A. Rothstein, *Keeping Your Genes Private*, SCI. AM., Sept. 2008, at 64.

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.

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

³⁰⁴ See Jack Hadley, *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.) 3, 38-41 (2003).

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 ETHICAL

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

PROBLEMS 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 Norman Daniels, *The Functions of Insurance and the Fairness of Genetic Underwriting* in GENETICS AND LIFE INSURANCE: MEDICAL UNDERWRITING AND SOCIAL POLICY 130 (Mark A. Rothstein, ed. 2004).

³¹¹ James M. Garner et al., *Medical Monitoring: The Evolution of a Cause of Action*, 30 ENVTL. L. REP. 10024, 10024 (2000).

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 experimental 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,

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., James F. Fries et al., *Beyond Health Promotion: Reducing Need and Demand for Medical Care*, 17 HEALTH AFF. 70, 70 (1998) (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 Robin Attfield, *Environmental Ethics and Intergenerational Equity*, 41 INQUIRY 207, 218 (1998).

³¹⁶ Stephen M. Gardiner, *The Real Tragedy of the Commons*, 30 PHIL. & PUB. AFF. 387, 402-03 (2002). See Stephen M. Gardiner, *Protecting Future Generations:*

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

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 Edward Page, *Intergenerational Justice and Climate Change*, 47 POL. STUD. 53 (1999).

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.

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 environment³²⁶ has not yet been explored to any substantial degree.

There is no widely accepted ethical argument with regard to intergenerational 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 intergenerational 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 contin-

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 Shobha Srivasan, Liam R. O'Fallon, & Allen Dreary, *Creating Healthy Communities, Healthy Homes, Healthy People: Initiating a Research Agenda on the Built Environment and Public Health*, 93 AM.J. PUB. HEALTH 1446 (2003).

ual 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

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 or

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

bloodlines 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.

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

³³⁶ BARBARA KATZ ROTHMAN, RECREATING MOTHERHOOD: IDEOLOGY AND TECHNOLOGY IN A PATRIARCHAL SOCIETY 115-16 (1989).

³³⁷ *Id.* at 57-58.

³³⁸ Martha A. Field, *Killing “the Handicapped”—Before and After Birth*, 16 HARV. WOMEN’S L.J. 79, 123-24 (1993); Erik Parens & Adrienne Asch, *The Disability Rights Critique of Prenatal Genetic Testing: Reflections and Recommendations*, 29 HASTINGS CENTER REP. (SPECIAL SUPP.) 1 *passim* (1999).

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

³⁴⁰ See Theresa M. Marteau & Harriet Drake, *Attributions for Disability: The Influence of Genetic Screening*, 40 SOC. SCI. & MED. 1127, 1130 (1994).

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).

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

³⁴² Theodosius Dobzhansky, *Man and Natural Selection*, 49 AM. SCIENTIST 285, 296 (1961).

³⁴³ ALLEN BUCHANAN ET AL., FROM CHANCE TO CHOICE: GENETICS AND JUSTICE 60 (2000).

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 indifference 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.

³⁴⁴ See Mark A. Rothstein, *Legal Conceptions of Equality in the Genomic Age*, 25 L. & INEQUALITY 429 (2007) (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”).