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Remembrance of Lives Past: The Challenge of Addressing Epigenetic Risk in Society

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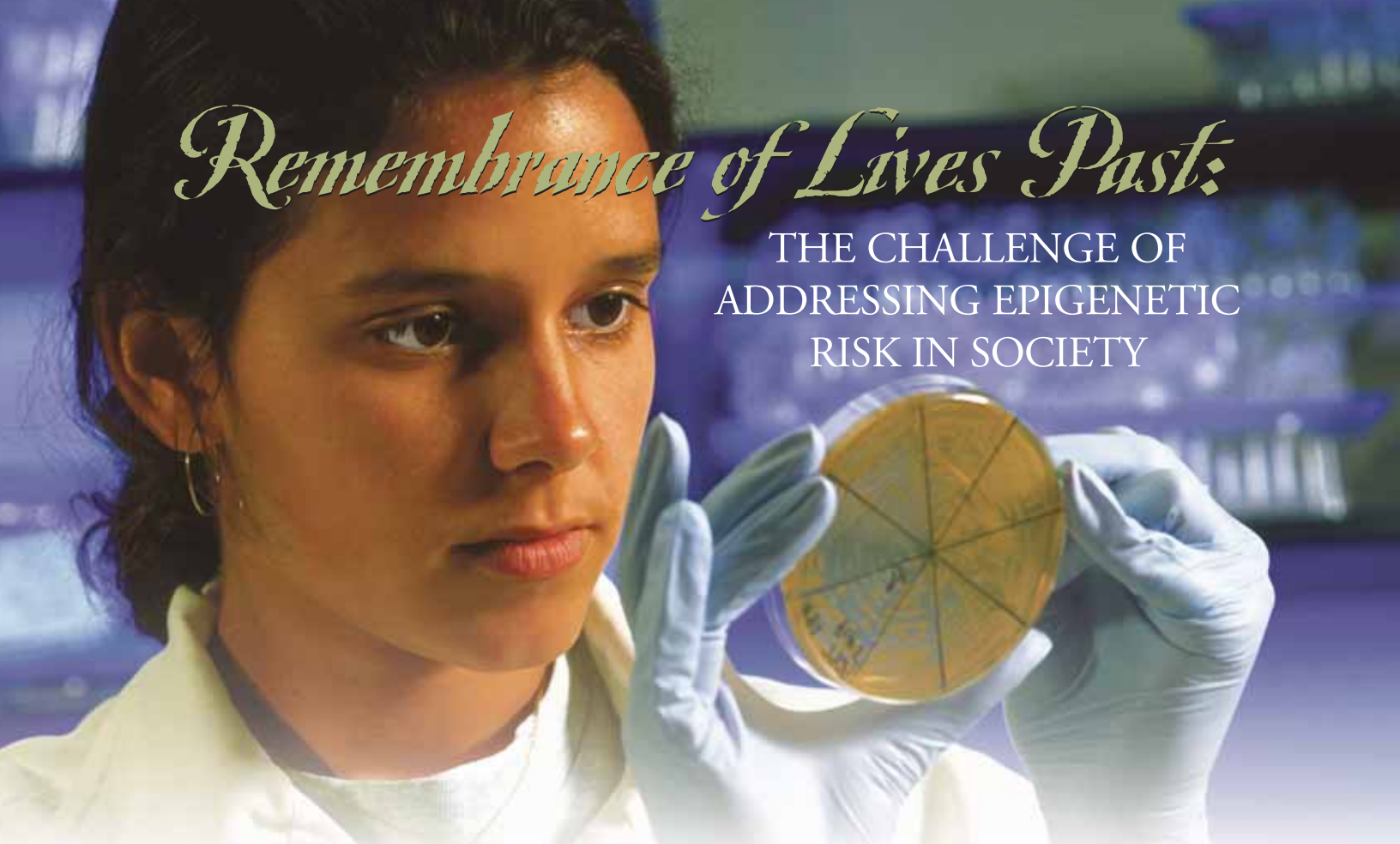


Remembrance of Lives Past:

THE CHALLENGE OF ADDRESSING EPIGENETIC RISK IN SOCIETY

Do our ancestors' experiences from several generations ago play a role in our current health? Could a famine or a period of food abundance experienced by our grandfathers affect whether we are currently obese or likely to develop diabetes? Can being the grandchildren of those who suffered through genocide or intense racial discrimination affect levels of certain chemicals in our brains even if we are not exposed to the same social stresses? In other words, do we biologically inherit the "memories" of past generations independent of changes to our ancestors' genetic code or DNA?

By Assistant Professor Fazal Khan

Surprisingly, according to rapidly growing research in the area of epigenetics, the answer to all of the questions above might be yes. Therefore, your diet, environmental exposures and social interactions could influence the health and behavior of your great-grandchildren.

As will be explained later, while epigenetics may predict head-scratching hereditary effects, understanding the science behind epigenetics is not that daunting.

What appear to be the more difficult questions are how do we develop policies to avoid the harms associated with epigenetic risk and *should we even attempt to do that?*

The implications of epigenetics are far-ranging and can affect the way we think about policies as widely divergent as product safety, environmental regulation, affirmative action and even the so-called "War on Terror." Given that our understanding of the science behind epigenetics is still relatively new and in a state of flux, it may not be prudent to suggest wholesale policy changes until we learn more about this biological phenomenon.

However, the preliminary findings in epigenetic research are too compelling to ignore.

Therefore, we need to invest more resources to assess the sources of harmful epigenetic changes and start considering policy frameworks to adapt to this knowledge in the most beneficial manner for our increasingly interconnected global society.

The Science of Heredity: Out with the New, in with the Old?

The hereditary theory of adaptation, as elucidated by Aristotle, Hippocrates and perhaps most famously by French biologist Jean-Baptiste Lamarck, held that the physiological changes acquired over

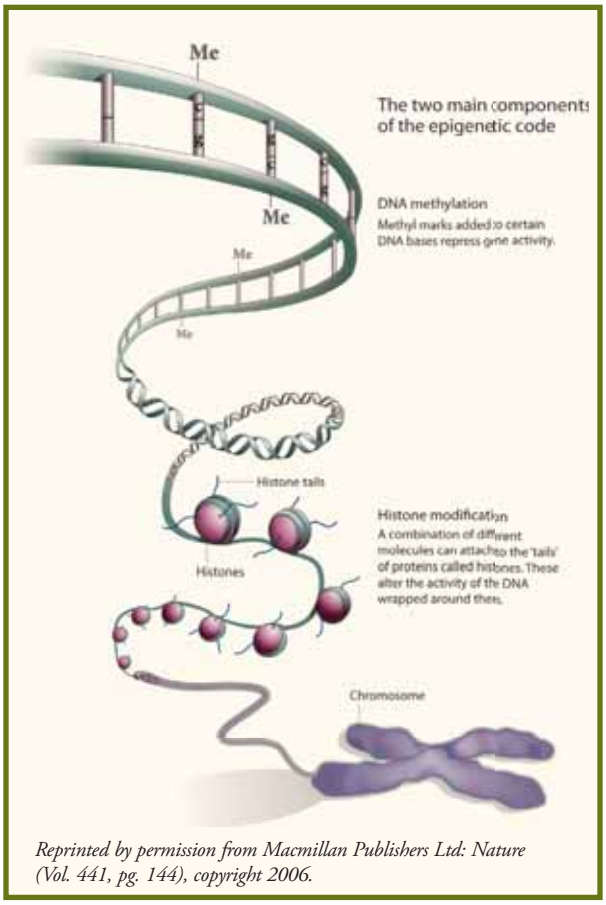
the life of an organism (such as a giraffe stretching its neck to reach the top of a tree or a watchmaker developing fine motor skills) are transmitted to their offspring.

This concept of inheriting acquired characteristics was firmly rejected after the acceptance of Charles Darwin's theory of evolution and gene-based inheritance.

Classic genetic theory holds that one's DNA sequence contains genes that code for proteins which in turn determine our biological fate. Therefore, under this concept, a future generation's biological fate is determined largely by its ancestors' DNA sequences and not at all by their ancestors' experiences (excepting, of course, if an exposure, to say radiation or a mutagenic chemical, changes the underlying DNA sequence which then gets passed on in an altered form).

As the Human Genome Project came to its conclusion, it gradually dawned upon scientists that the study would not answer all of the questions they initially believed it would.

For instance, researchers expected to discover at least 100,000 genes in the human body. However, they only found a fraction of this number – less than 30,000.



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Certain diseases with an observable hereditary linkage, such as diabetes, did not have an identifiable gene associated with it.

Further, we know that identical twins possess the exact same DNA, but genetics alone does not explain how one twin can develop a hereditary disease while the other one does not.

Slowly, scientists began to consider the previously discarded notion that we inherit more than just genes.

Epigenetics is different from Lamarckism (the passing on of characteristics that one acquires during its lifetime to offspring) because it accounts for the concept that gene coding for certain traits are passed down to subsequent generations.

The basic science of epigenetics is that chemicals attach to our DNA directly, or the DNA's protein backbone, and act to alter the expression of these genes. Essentially, epigenetics adds a whole new layer of information to genes beyond the DNA sequence itself.

Imagine a control system of switches that turns the genes you possess on or off. Therefore, under this model, if you merely possess a gene that codes for disease X, it is not certain that you will develop disease X if an "epigenetic marker" (a chemical attached to DNA) switches this disease-causing gene off.

Conversely, an epigenetic marker can switch off a helpful tumor-suppressing gene (i.e., a cancer fighting gene) in your body and thus increase your susceptibility to cancer.

This process is different than an environmental exposure mutating your DNA, because with epigenetic marking, the preexisting DNA code remains intact.

So what is the big deal about epigenetics? Almost everyone has an understanding that external exposures (nurture) in combination with our genetic predisposition (nature) determine our biological development and health status.

For example, many people with a family history of cancer seek organic foods stemming from the fear that chemical exposures can push their pre-existing risk for cancer over the "tipping point."

The big deal, or bizarre part of epigenetic theory, is that the pattern of DNA "marking" that you acquire during your lifetime can be passed on to subsequent generations – thus your acquired experiences can affect how your great-grandchildren's DNA is expressed without them having the exposures that caused your particular pattern of epigenetic markings.

Of Mice and Men – or Honey, I Blew Up the Grandkids?

Dr. Randy Jirtle, a cancer researcher at Duke University, developed an elegant research model to demonstrate how epigenetic mechanisms operate.

He began with mice that contain the agouti gene. This gene makes agouti mice over-consume food, have yellow fur, be cancer-prone, be diabetes-prone and have a dramatically shortened lifespan.

Breeding two agouti mice together invariably results in offspring having agouti physical characteristics – most noticeably being yellow and obese.

However, Jirtle was able to breed two agouti mice together whose offspring were thin and mousy brown. More importantly, these agouti offspring did not possess their parents' propensity to develop cancer or diabetes and were blessed with a normal lifespan. In essence, the effect of the agouti gene had been turned off.

Not knowing any more information, one might assume Jirtle performed genetic engineering on the mice – however, the offspring still contained the agouti gene of their parents with the DNA sequence intact.

His intervention was surprisingly much simpler. He simply changed the mothers' diets.

Right before conception, the test group of maternal mice was fed a diet filled with methyl-donors, molecules that are common in foods such as onion, garlic and beets.

Methyl is a small chemical molecule (CH_3) that can attach to a gene and turn it off like a light switch.

As the pregnant mothers ate this diet, the methyl-donor molecules were passed into the developing embryos' DNA code and specifically onto the agouti gene. The agouti gene was passed onto the offspring unchanged, but it now contained a chemical dimmer switch that blocked the harmful effects of the gene. Furthermore, these epigenetic changes could now be passed on to subsequent generations of offspring.

In another rodent study, Washington State researchers found harmful epigenetic changes related to toxic fungicide or pesticide exposure can persist in rat offspring for at least four generations even though subsequent generations were not exposed to these harmful chemicals.

But mice are not men. Do we see the same mechanism in humans?

In 2005, European researchers presented an intriguing study that looked at two centuries of crop yields and food prices for a geographically isolated town in Northern Sweden. The researchers discovered that fluctuations in the locality's food supply influenced health outcomes spanning at least two generations.

Specifically, grandfathers who lived their pre-adolescent years during times of bountiful food supply were more likely to have grandsons with diabetes – *doubling* these grandsons' risk of early death. Even more telling, grandsons of grandfathers who experienced plenitude during the pre-pubescent "slow-growth" period of sperm development were the most affected.

This finding is particularly important for public health officials because we are currently facing an epidemic of obesity and diabetes in our country.

The most common explanation for this epidemic is that we are sedentary couch and desk-potatoes, surfing the day away on the Internet or TiVo, all while consuming sugar and fat-laden processed foods in sumo-sized portions.

However, regarding childhood obesity in particular, public health experts have studied every imaginable intervention – including healthier school lunches, more physical education and more nutrition training.

To everyone's frustration, none of these common-sense strategies have been shown to have a significant effect in combating childhood obesity.

The lingering question is what if our obesity epidemic is a reflection of lifestyles adopted by our grandparents?

Crime and Punishment: Are We Haunted by the Ghosts of Our Past?

Belief in the existence of ghosts, especially of deceased family members, is common across many different cultures. This belief reflects the notion that our ancestors have a continued existence and possess the ability to influence the destiny of the living.

In a sense, epigenetics provides a molecular basis of how our ancestors' lives, not their genetics, continue to shape the fortune of the living long after their death.

What is particularly troubling is that this may mean that the crimes of our past, whether it be genocide, racism or unbridled militarism, can continue to punish us long after these actions have ceased.

One rat study demonstrated that how a mother nurtures her pups determines the offspring's behavior as adults.

Rat pups which were licked more by their mother became more assertive in social interactions and were calmer when startled. The neglected pups, on the other hand, developed into adults who were more passive and reacted nervously when startled or placed in unfamiliar settings.

Cortisol is a hormone that is released in the brains of many animals (including humans) in response to stress.

The "licked rats" developed epigenetic markers that removed dimmer switches on a gene that regulates cortisol release. In a sense, the licked rats had a better developed "stress thermostat," which translated into them being less anxious and better able to cope in stressful situations.

The neglected rats did not develop this regulatory gene to the same extent, which led them to overproduce cortisol in response to stress, thus amplifying their anxiety.

Therefore, we can see that the mother's nurturing behavior did not simply affect her offspring's behavior, it physiologically altered the functioning of the stress regulation gene inside the brain. Additionally, these changes were stable throughout adulthood in the rats.

This study is significant because it demonstrates that epigenetic markings on the DNA change in response to parental care.

As a follow-up, scientists at McGill University focused an epigenetic lens on men who were abused physically, sexually, mentally or a combination of all three as children.

All of these men committed suicide, and their brains were compared to men who also suffered abuse but died of natural causes.

The researchers found that childhood abuse alters the typical chemical marking of DNA in the brain.

In the suicidal men, the gene that regulates the release of the stress hormone cortisol was less active. The researchers speculate that the men's brains were hardwired to have problems coping with stress as adults, which then contributed to their suicides. Basically, childhood abuse "communicates" to the genome to alter the molecular structure of the brain.

However, the two studies discussed earlier do not address the question of whether these molecular changes are passed on to subsequent generations.

Researchers are now attempting to answer that question by looking at women who were pregnant during extremely stressful times, such as wartime or during the 9/11 terrorist attacks and to see if changes in stress regulation can pass down to future generations – their preliminary answer is yes, and the implications for social policy makers are dramatic.

Child-parent bonding is much more difficult in an environment of poverty, social unrest or even lack of childcare services for working parents.

These factors can affect the cognitive development of the children involved and potentially might affect the development of future generations through persistent epigenetic markings.

Dr. Lawrence Harper, a research psychologist at the University of California at Davis observes that personality attributes, such as temperament and intelligence, can be impacted by epigenetic inheritance: "If you have a generation of poor people who suffer from bad nutrition, it may take two or three generations for that population to recover from that hardship and reach its full potential."

In other words, because of epigenetic inheritance, it may take several generations to erase the harms from a variety of social ills such as poverty, war, dislocation or intense discrimination.

Perhaps this might lead supporters of eugenic (or hereditary) arguments as expressed in controversial books like *The Bell Curve* to reconsider their belief that certain minority groups are genetically predestined to have lower intelligence capabilities and be at the bottom of the socio-economic ladder.

Further, in prosecuting the "War on Terror," we might reconsider whether using overwhelming military force and supporting politically repressive regimes over a long period of time really guarantees our country a peaceful future.

The "blowback," or unintended negative consequences of our foreign policies both at home and abroad, might last longer than we think.

Regulating Epigenetic Risk from Consumer Products

So how should epigenetic risk be regulated in society? Some sources of epigenetic risk (violence, discrimination, etc.) are so diffuse and complex that they may not be amenable to simple legal or rule-based solutions.

However, if an epigenetic risk factor can be traced back to a particular manufactured product or activity, it seems that a legal or policy response would be feasible.

Our first thought might be to use the tort system to regulate this risk in the same way we use tort liability to deter the production of harmful substances or activities.

For several reasons, the tort model is not ideal to address the issue of epigenetic risks and harms.

One problem is evidentiary. Plaintiffs in most tort cases have the burden to prove their case by a preponderance of the evidence (more than 51 percent probability). However, given the multi-factorial genesis of diseases that may be influenced by epigenetic causes, it would be difficult to ascribe more than 51 percent of the blame to a single offending product that increased one's epigenetic risk.

Further, the parties with the most information and capability to do research on epigenetic risk, the manufacturers of consumer goods, have no incentive to uncover such risks.

As discussed by many toxic tort scholars, without external regulation, it is generally in the interest of corporate managers to remain ignorant of undiscovered liability.

The reasons for this are simple. The cost of doing research on undiscovered risks is real and will be borne in the present during the current company executive's tenure, but the benefit in terms of avoiding potential liability is uncertain and would accrue in the future, after the present-day executive has left his position.

Another major problem with assessing liability for epigenetic harms is that the injury is often indirect (the offending exposure might have occurred to your grandfather and not you) and latent (the harm may not be apparent until many years after the exposure). Therefore, potential plaintiffs will likely have problems proving their case by a preponderance of the evidence, identifying the correct defendants and filing a claim within the time period required by the statute of limitations or repose.

At least regarding the statute of limitations, one might argue that the "discovery rule" may be invoked, which allows plaintiffs to suspend the running of the limitations period until the cause of the injury should have been realized or discovered. However, a statute of repose will likely also apply, which would bar a legal action a certain number of years after when the product was initially delivered, regardless of when the injury was discovered.

If the latent harm spans a couple of generations, the statute of repose would surely ban such an action – and with good cause.

Do we really want to hold the manufacturers of products liable for harms for an indefinite period, especially if such harms were unforeseeable at the time of production?

If a manufacturer stopped producing the offending product many years ago, relaxing statute of repose laws to account for epigenetic causation would not satisfy any deterrent role and may only serve to punish a party that might be producing entirely unrelated, and perhaps beneficial, products.

So, if we accept that the tort system is ill-equipped to deal with harms stemming from epigenetic risks, how can we deal with this problem?

The Epigenetic Taxman Cometh: A Strategy to Incentivize Manufacturers to Itemize the Epigenetic Risk They Create

As U.S. Court of Appeals Judge Guido Calabresi pointed out in his seminal work *The Cost of Accidents*, we, as a society, do not always want to reduce the number of accidents to zero.

We knowingly tolerate more than 40,000 deaths from auto accidents every year because, in order to significantly lower this number, we might have to drive cars with tank-like armor that are slower, less fuel efficient and much more expensive.

The market may support paying higher costs for certain safety interventions (for example, airbags) if the perceived or real benefits outweigh the costs but not for other interventions (e.g., tank-like armor) if the perceived costs outweigh the benefits.

As we learn more about epigenetic risk caused by certain

products, we might discover that some very beneficial products, like pharmaceuticals or useful consumer goods (e.g., plastic water bottles) contribute to epigenetic risk.

The question then becomes how do we reach the optimal level of use of products that cause such harm?

"Externalities" are broadly defined by economists as effects (whether positive or negative) on unrelated third parties that are not involved in a given transaction.

If the externality is negative and causes harm to unrelated third parties, then the transacting parties are not bearing all the costs of their activities. For example, if you buy cheap electricity from a producer that cuts costs by not installing pollution control equipment, then you and the producer are passing on externalities to the public in the form of air pollution.

The goal of regulation would be to have the parties *internalize* the costs of their externalities.

This could be done by the government fining excessive pollution producers or forcing them to install pollution capturing equipment – both interventions force the producers to spend more to produce their energy, thus internalizing the cost of their activity. The producer will pass this added cost to end-consumers forcing them to internalize the cost as well.

If demand is price sensitive or elastic, then you will also observe less consumption of this good after the cost of its externalities are internalized.

If demand is inelastic, meaning that people value the good so much that the higher price will not affect their purchasing decision, the good will be consumed at the same level.

In this way, by using both regulation and market forces, society can get to the optimal utilization of a product.

The particular problem with this type of regulation, in light of our ignorance about the epigenetic risk profiles of manufactured products and activities, is that unwittingly we may be experiencing massive market failure in the form of over-consuming products whose ultimate harms outweigh their utility.

So how do we overcome our ignorance regarding epigenetic risks?

A major impediment is that actors generally resist uncovering information regarding the adverse effects of their products or activities.

As previously discussed, research into the potential harms of your activities is not only costly but can open the door for more liability – thus one's incentive is to remain ignorant.

This is where it seems the government should step in and change the incentive structure so manufacturers will develop information regarding the epigenetic risk they are creating.

One method for doing this is having a government agency intentionally overestimate the epigenetic risk of certain "suspect" products and levy an "epigenetic tax" on products or activities based upon the amount of estimated epigenetic liability created.

These taxes will add to the product's cost commensurate with the estimated risk, thus internalizing the cost of harmful epigenetic externalities.

This strategy would give industry a strong incentive to conduct its own objective epigenetic research to rebut the government agency's presumption, and thus lower the amount of taxes it pays.

Therefore, this approach would mirror the familiar model of the government withholding taxes from an individual's wages and the individual filing for a refund after determining his or her actual liability was lower than the government estimated.

An important wrinkle we have to consider, given the agouti mice experiment, is that epigenetic risk is possibly reversible through certain treatments.

Indeed, a start-up biotech firm in Canada is currently testing the first epigenetic-based cancer therapy.

The potential mitigation or reversibility of epigenetic risk would then play a role in how we measure the attendant risk of a product or activity.

If its harms can be reversed, then we safely consume more of this product as a society.

Once again, with the epigenetic tax system, we see that manufacturers have an incentive to fund research for therapies aimed at mitigating or reversing the effects of their actions, if it will lead to lower levied costs and thus more consumption of their products.

Conclusion: Am I My Grandchildren's Keeper?

While still very inchoate and rapidly growing, our understanding of epigenetic mechanisms represents a dramatic paradigm shift in scientific thinking. It alters our conception of disease causation and the influential role played by our lifestyles and social relationships.

In a real sense, we are the caretakers of our genome, and our actions will affect the health of our children and grandchildren for many years into the future.

The broad metaphysical question that arises then is what duty do we owe them? Does contemporary society have to constrain its actions to protect future generations? Would such a vague notion of societal responsibility run afoul of our society's reverence for individual autonomy and liberty?

Further, if we simply constrain our manufacturers' actions, are we really protecting ourselves in a globalized world where many of our products are sourced from abroad? In addition, are we placing our corporations at a competitive disadvantage compared to companies in developing countries like India or China?

These developing countries may argue that worrying about epigenetic risk (much like worrying about global climate change) is something they will have the luxury to consider only after they reach a level of development close to that of the United States and Europe.

Thus, as we learn more about the sources of epigenetic risk, it will likely be regarded as a global problem much like climate change (perhaps inspiring a global cap and trade system for epigenetic risk akin to the model for carbon emissions?).

Ultimately, as we learn more about the science of epigenetics, the policy discussion will encompass a wide array of disciplines, from law and medicine to business and politics.