The ambiguous nature of epigenetic responsibility

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ABSTRACT

Over the past decade, epigenetic studies have been providing further evidence of the molecular interplay between gene expression and its health outcomes on one hand, and the physical and social environments in which individuals are conceived, born and live on the other. As knowledge of epigenetic programming expands, a growing body of literature in social sciences and humanities is exploring the implications of this new field of study for contemporary societies. Epigenetics has been mobilised to support political claims, for instance, with regard to collective obligations to address socio-environmental determinants of health. The idea of a moral ‘epigenetic responsibility’ has been proposed, meaning that individuals and/or governments should be accountable for the epigenetic programming of children and/or citizens. However, these discussions have largely overlooked important biological nuances and ambiguities inherent in the field of epigenetics. In this paper, we argue that the identification and assignment of moral epigenetic responsibilities should reflect the rich diversity and complexity of epigenetic mechanisms, and not rely solely on a gross comparison between epigenetics and genetics. More specifically, we explore how further investigation of the ambiguous notions of epigenetic normality and epigenetic plasticity should play a role in shaping this emerging debate.

The rapidly growing research field of epigenetics has recently inspired some scholars to address the potential implications of this new scientific knowledge for contemporary societies. Expectations of medicine and public health have risen as a result of a greater understanding of the relationships between living conditions, lifestyle, gene expression and health. The ethical, legal and social concerns related to epigenetics research have been discussed in the literature, building on principles of ‘environmental justice’, ‘intergenerational equity’, ‘equitable access to healthcare’ as well as ‘privacy and confidentiality’.1 Normative discussions have emerged, pointing out how recent findings in epigenetics concern moral responsibility in relation to health.

In this paper, we argue that important nuances in the nature of the epigenome may be underestimated in some of these normative inquiries, especially when attention remains focused mainly on the differences and similarities between genetics and epigenetics. This way of framing the ethical debate—that is, understanding epigenetics and its consequences for society as ‘opposed to’ or ‘not so different from’ genetics—fails to address important differences that exist between various types of epigenetic mechanisms and variants and may thus misconstrue the debate surrounding moral epigenetic responsibilities. We argue that to date, the impact on the identification and assignment of moral epigenetic responsibility by two important ‘biological ambiguities’ within the field of epigenetics—epigenetic normality and epigenetic plasticity—has not received enough attention in the bioethics literature.

First, defining ‘epigenetic normality’ is significantly complicated by some of the biological features of the epigenome: its non-uniquity among cells and tissues, the fact that it is actively reshaped during pregnancy, infancy and adulthood, and the theory according to which epigenetic programming would be a way of adapting to the living environment. We argue that a more comprehensive understanding of the notion of ‘normal’ or ‘reference’ epigenome is required prior to determining personal and collective goals regarding epigenetic health. Second, epigenetic modifications can be both plastic and potentially heritable, two features that seem contradictory. Addressing this tension is a prerequisite to discussions of epigenetic responsibility, since the level of plasticity of a specific detrimental epigenetic variant may impact one’s capacity to prevent and/or reverse that variant. This, in turn, would impede the legitimacy of ascribing moral responsibility for interventions that target such variants.

This paper aims to caution the bioethics community against adopting a simplistic approach toward ‘epigenetic responsibility’. It aims to broaden future discussions towards an assessment of multiple types of ‘moral epigenetic responsibilities’. Building on scientific nuances in the biology of epigenetic mechanisms, we anticipate and present few ethical and legal perspectives seemingly emerging from recent epigenetic findings. We thus aim to provide a conceptual clarity for such discussion, one that distinguishes between various types of epigenetic responsibility, rather than one that sees it emerging mainly in terms of the comparison between epigenetics and genetics.2–7

TOWARDS MORAL EPIGENETIC RESPONSIBILITIES

Learning from genetic responsibility

Rapid improvements in sequencing technologies and the performance of genetic testing has resulted in the controversial notion of genetic responsibility.8–11 It has been argued that the predictive nature of genetic information should be considered a valuable additional tool for empowering at-risk

The word ‘normal’ is used in its statistical sense (i.e. the middle section of the Gaussian normal bell curve) and should be understood as morally neutral.

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individuals who are now able—and possibly ought—to adopt ‘life strategies’ that are in line with their genetic susceptibilities, in order to prevent disease and optimise health. More specifically, narratives of responsibility have emerged in contexts such as a patient’s choice whether to disclose potentially useful genetic information to family members or prospective parents’ alleged moral responsibility to consider their genetic profiles before conceiving, or to use prenatal testing, in order to give birth to the healthiest child possible. Consequently, the implementation of genomic sciences into healthcare demonstrated how molecular explanations of disease—and the availability of new biomedical means to prevent or treat it—can contribute to the construction of novel imperatives for different actors in society.

In contrast with the genome, epigenetic mechanisms and variants are determined partly by living conditions and lifestyle. Modifications to the three-dimensional structure of DNA at specific genes in specific cells influence gene expression and thus health. Changing the level of accessibility of the transcriptional machinery to some genes has an effect on the subsequent production of proteins that tissues need in order to execute their normal biological functions. By connecting external and internal environments to genes, epigenetics has been perceived as a revolutionary field of study. Anthropologists, for instance, have claimed that recent findings in epigenetics are transforming the long-standing ‘nature–nurture’ debate that traditionally focused on them as two distinct sets of determinants of identity, behaviour and health. They argue that epigenetics demonstrates the fallacy of this dichotomy:

In an epigenetic world, recognition of intergenerational continuities other than by the transmission of DNA brings about a crucial ontological shift; an embedded body is not the product of interactions of nature and nurture but, by definition, is situated in an entanglement of nature/nurture that transcends generations, raising profound questions about concepts of self and body as clearly bounded entities.

The adaptive nature of some epigenetic modifications and their transgenerational inheritance have also contributed to epigenetics being labelled as revolutionary. These features have revived the discarded Lamarckian theory, according to which an organism’s acquired trait and biological adaptation to its environment can be biologically passed on to future generations through germ cells.

So far, ethical and legal discussions regarding epigenetics have been framed mainly in terms of comparisons between the fields of epigenetics and genetics. For instance, Rothstein has argued that while epigenetic changes may to some extent be exceptional when compared with genetic variants at the scientific level (high frequency of occurrence, dose-dependent, reversible, tissue-specific and species-specific), they are not that exceptional from an ethical and legal perspective and require no ‘new ethical paradigm [or] legal regime’ (p. 714). Already existing legal frameworks such as environmental regulations and the U.S. Federal Genetic Information Non-Discrimination Act of 2008 (GINA) may be sufficient, he argues, for addressing the concerns that arise with epigenetics (such as environmental justice, intergenerational equity, equitable access to healthcare, privacy and confidentiality).

While we agree that epigenetics does not necessarily require a novel ethical framework, we argue that the normative accounts of epigenetics do require a heightened degree of bioethical attention, especially considering its potential impact on the political theory of the family and its relation to social justice as well as intergenerational justice. In fact, epigenetics opens a much wider range of opportunities for health intervention than genetics have in the past. In contrast with genetic mutations, detrimental epigenetic variants may be more easily preventable or curable, because they are plastic and reversible. While genetics are mainly determined by biological inheritance—something upon which individuals and society have little direct control—a better understanding of epigenetic programming could imply new opportunities to improve individual and public health—and thus more control and arguably new obligations. Hence, it reveals a set of moral agents (eg, individuals, parents, corporations, governmental agencies, international organisations) that could to some extent be held morally accountable for epigenetic health, and consequently significantly broadens the range of possibilities for holding these agents accountable for voluntary negligence when it results in epigenetic harm to others.

Moral epigenetic responsibilities

Epigenetics is already the object of bioethical attention, which has shed light on ‘individual and societal responsibilities to prevent hazardous exposures, monitor health status and provide treatment’, p. 224. As observed by Landecker, ‘[t]he normative implications of a science that draws direct causal links, at the molecular level, from such culturally tender and politically contested issues as parenting and air quality regulation to human health are a subject of much speculation in this field’. At the policy level, epigenetics was suggested, for instance, to feed a ‘social work imperative’ meaning that it should justify and encourage ‘a mandate for social workers to intervene at the policy level, both for today’s children and for those in future generations’. At the clinical level, the malleability and reversibility of some detrimental (or risky) epigenetic variants arguably call for further techno-scientific innovation as well as the creation of new types of biomedical interventions to ‘cure’ the epigenome of at-risk individuals.

Political scientist Maria Hedlund explores the concept of epigenetic responsibility, building on four important conditions for ascribing moral responsibility. She claims that in order to be morally responsible for adverse consequences related to epigenetic health, one must be causally responsible for a certain epigenetic variant, be morally responsible for adverse consequences related to epigenetic health, and be able to do what is morally required in order to achieve that ideal (the capacity criterion). Political scientist Maria Hedlund explores the concept of epigenetic responsibility, building on four important conditions for ascribing moral responsibility. She claims that in order to be morally responsible for adverse consequences related to epigenetic health, one must be causally responsible for a certain epigenetic variant, be morally responsible for adverse consequences related to epigenetic health, and be able to do what is morally required in order to achieve that ideal (the capacity criterion). Building on these criteria, Hedlund argues that epigenetic responsibility should be primarily prospective, rather than retrospective—that is, oriented towards guiding future actions rather than assigning blame for past actions—and be ascribed primarily to the State, rather than the individual.

Unfortunately, Hedlund’s account of epigenetic responsibility has a number of flaws limiting its utility as a framework for identifying and assigning various types of moral epigenetic responsibility among different actors of society. While we are aware of—and concerned with—the ethical pitfalls of ascribing epigenetic responsibility to individuals, we argue that defining epigenetic responsibility as a priori prospective and belonging mainly to the State is misleading because it is simplistic, ineffective and ethically problematic. It is simplistic because it reduces discussion to the tension between the citizen and the State,
whereas other actors may have a role to play (eg, corporations, international organisations). It is ineffective because attributing mere prospective responsibility without the possibility of holding actors responsible for past negligence (through health policies or laws) may result in a very limited upholding of the suggested prospective responsibility. It can be ethically problematic in the sense that ascribing epigenetic responsibilities entirely to the State fails to recognise that overpaternalistic health policies run the risk of turning into coercive measures threatening individual autonomy.

It is oversimplistic to understand epigenetic responsibility as a monolithic concept emerging solely from comparisons between epigenetics and genetics. Such understanding fails to take into account important scientific nuances within the field of epigenetics itself that should be incorporated into the debate. For this reason, we offer an ethical perspective that addresses the diversity of types of epigenetic responsibility. We argue that this diversity is likely to emerge from future developments in epigenetics. Using Hedlund’s criteria for assigning moral responsibility (causation, cognisance, obligation and capacity), we make the assumption that in the near future, the two first criteria will be fulfilled, that is, there will be some agreement in the scientific community that specific types of epigenetic programming can be causally responsible for the development of disease (causation) and that this knowledge will be successfully disseminated to the larger public (cognisance). Our framing thus focuses on the last two criteria and underscores two important ‘biological ambiguities’ inherent to epigenetic mechanisms themselves: ‘epigenetic normality’ (in relation to the criterion of obligation) and ‘epigenetic plasticity’ (in relation to the criterion of capacity). These ambiguities have already been reported and discussed by social scientists but their important normative relevance has been largely overlooked.

EPIGENETIC NORMALITY AND THE OBLIGATION CRITERION

Thanks to epigenome-wide association studies (EWAS) and vast collaborative projects such as the US National Human Genome Research Institute (NHGRI) Encyclopedia of DNA Elements (ENCODE), the US National Institutes of Health (NIH) Epigenomics Roadmap and the International Human Epigenome Consortium (IHEC), researchers have recently undertaken the tremendous task of characterising the human ‘reference epigenome’, that is, the ‘methylome’, the ‘histone acetylation code’—considered to be the major portion of a larger ‘histone code’—and the ‘non-coding RNAome’ (cf. 26). The expected outcome of these ambitious investigations consists largely of a better understanding of the role of epigenetic mechanisms in normal human functioning and the development of disease.

Defining epigenetic normality

The above-mentioned studies are expected to generate a list of detrimental epigenetic variants that may provide causal links between living conditions and health/disease. By mapping these ‘harmful’ variants, these studies determine what a ‘reference’ or ‘normal’ epigenome is, that is, what epigenome is associated with health or at least not associated with specific diseases. Notwithstanding the promising preventive and therapeutic opportunities that this endeavour may provide—and accordingly its potential implications for assigning novel responsibilities for epigenetic health—defining epigenetic normality (and by extension abnormality) is scientifically and ethically challenging for many reasons.

At least three biological features of the human epigenome contribute to making its characterisation an even more daunting task than the Human Genome Project represented 20 years ago.

First, in comparison to genomic information which is unique and ubiquitous in all the cells of an organism, each cell line—thus each tissue and biological system—has its own epigenome. Second, as will be discussed more extensively in the next section, the multiple epigenomes of an individual are relatively plastic and subject to multiple modifications that depend on various factors (eg, prenatal environment, lifestyle, age). Third, epigenetic variants interact with each other and are highly influenced by the microenvironment in which these interactions take place, that is, on variations in the microstructure of chromatin at specific loci. Considering these biological features, it becomes a very complex endeavour to define the reference epigenome, and before judging the level of normality of someone’s epigenetic programming, the larger context of its occurrence (eg, cell type, age of the person, microenvironment surrounding the variant) must be understood with precision.

The mismatch model of disease development

Another—possibly greater—challenge of characterising epigenetic normality is caused by the ‘mismatch model’ of epigenetic disease development. According to this model, an adverse phenotype does not depend merely on the presence or absence of a specific epigenetic variant, but rather on the mismatch between the previously programmed variant and the individual’s lifestyle or living conditions. In other words, the early programming of some distinct epigenetic patterns is sensitive to the developmental environment and aims to better prepare the organism for the environment it will most likely be surrounded by in the future. The mismatch model of disease has been suggested to account for the fact that a specific lifestyle or living condition can be more or less detrimental to different individuals and populations, depending on the environment in which the early epigenetic programming occurred.

The mismatch model was corroborated mostly by experiments on obesity. It was suggested that the epigenetic programming of obesity-related genes during fetal development was influenced by the availability of nutrients in the womb during pregnancy: that is, low nutrient availability would result in a programmed increased efficiency of the body for storing calories in the lipid tissues later in life, in order to optimise their uptake and use. Subsequently, if the environment changes during the life course and nutrients become more available and diets become richer in calories, this epigenetic programming may become disadvantageous and lead to a higher risk of obesity and its associated metabolic syndromes. In other words, epigenetic programming can be perceived as an active biological mechanism that aims to increase an individual’s ‘fit’ to her surrounding environment. At the same time, this programming can become maladaptive when the environment changes and thus become detrimental to health.

Consequently, it appears that when taken individually without consideration for their environment, epigenetic variants are unreliable biological markers for disease susceptibility and epigenetic normality cannot be regarded as universal. Rather, epigenetic normality has to be rooted in geographical and temporal references that are specific to individuals and populations. For this reason, it is often unclear whether epigenetic differences—potentially perceived as epigenetic abnormalities—should be treated as impairments or rather functional adaptations conferring advantages in specific environments.
Personal and public health ideals

The biological features of epigenetic mechanisms discussed above and the mismatch model of disease development introduces significant complexity to the task of defining and ascribing epigenetic responsibilities. Central to this difficulty are important questions that need to be addressed in order to determine what kind of epigenetic ideal we ought to pursue, individually and collectively, using preventive or therapeutic means, and whether we should pursue such an ideal at all. Such questions may impact the construction of different types of novel personal and collective obligations.

For instance, should public health policies aim at favouring the programming of a specific epigenome that best corresponds to that of the majority or should physicians cure deviations from it? Should we consider the idea of a normal epigenome to necessarily be bound to that of a healthy epigenome? And what could the normative implications of such simplistic associations be? Should we focus on the best environment for the healthy programming and maintenance of epigenetic health or rather promote programming the epigenome so that it best matches the living environment or lifestyle of the individual? These questions should be debated, since each may lead to distinct ethical, legal and social implications that we must anticipate before defining and ascribing moral epigenetic responsibilities. We argue that the three examples presented below require ethical attention.

First, aiming for the ‘typical epigenome’—the one that is found in most people in a given population—may be misleading. Indeed, we should be careful not to conflate the atypical epigenome with the detrimental one, or the one that requires intervention. For instance, it was suggested by Rice et al.\(^{35}\) that homosexuality could in part be explained by epigenetic mechanisms during development and ‘atypical’ epigenetic variants associated with distorted prenatal androgen exposure. Needless to say, such findings are very sensitive, since they frame sexual orientation in medical terms. Using the language of biology to discuss homosexuality, we are at great risk of falling into a ‘normal versus abnormal’ debate that could undermine the human rights framing that focuses on protecting individual autonomy and promoting the standing of sexual minorities. In order to avoid simplistic conclusions with regard to the typical epigenome, we should keep in mind David Hume’s naturalistic fallacy and be careful not to derive too hastily an ‘ought’ from an ‘is’.

Second, in a context of resource scarcity, the development, implementation and promotion of public health measures that would target particular epigenomes, perceived as an ideal public health goal, might become grounds for discriminating (and potentially eugenic) policies and behaviours. For instance, it was argued that the potential for transgenerational inheritance of some epigenetic variants may be used as an additional argument for the development of sustainable obesity prevention policies.\(^{16} \) Hence, those desiring to have children, but carrying an epigenetic variant (acquired or inherited) recognised to increase one’s risk for obesity and transferable to future generations, could be discouraged from—or in the worst case prohibited from—procreating, in order to improve future public health. While we agree that epigenetics may and eventually should contribute importantly to the implementation of more effective and ethically sound health policies, we also need to remain aware of the potential ethical pitfalls of such policies. To some extent, health promotion aiming for the healthy epigenome risks exacerbating social pressure on individuals to optimise, for instance, their offspring’s epigenetic programming so that they meet the social norm. Ultimately, this may lead to stigmatisation and discrimination of those whose epigenomes differ significantly from the socially desired or expected ones.

Third, while it may seem wise to consider both the epigenome and its environment when defining social obligations and orienting health interventions, the mismatch model may undermine the implementation of health policies aiming to facilitate the adoption of healthy lifestyles and favouring fundamentally healthy living conditions widely recognised as contributing to the programming of healthy epigenetics (eg, enhancing food availability or socio-economic status in general). In some way, the mismatch model defines ‘normal’ epigenetic programming as functional adaptation to the environment. Speculating regarding such a capacity, how important is it to improve people’s living environments through public health policies? The mismatch model may lead to the troubling implication that by trying to improve the social circumstances of disadvantaged groups, we risk making their health even worse. For instance, populations moving from low to high caloric intake may be more susceptible to obesity and its associated diseases, because their metabolism was ‘epigenetically programmed’ to stock calories in an extremely efficient way. Consequently, the mismatch model may devalue requirements for health policies and could be exploited to justify existing environmental and social injustices. One might argue, for instance, that governments and public health agencies should not intervene to improve the epigenetic programming of disadvantaged populations, because this biological mechanism ‘naturally’ prepares them for facing adverse living environments later in life.

In sum, when trying to identify moral epigenetic responsibilities, a few important difficulties arise in relation to the complex concepts of ‘reference epigenome’, ‘epigenetic normality’ and ‘epigenetic ideals’. What healthy behaviour should individuals adopt if they do not even know what epigenome to strive for? In this context, on what grounds should epigenetics drive the creation and implementation of health policies? Most importantly, we argue, none of the different perspectives presented above should be taken for granted or be privileged *prima facie*. It is also necessary to recognise that epigenetic normality may be both scientifically and socially constructed, and that our definition and ascription of epigenetic responsibilities may vary according to the preferred perspective. For this reason, a simplistic view of epigenetic normality and associated moral epigenetic responsibility should be avoided.

EPIGENETIC PLASTICITY AND THE CAPACITY CRITERION

Compared with genetic modifications, epigenetic modifications are very dynamic biochemical reactions. This feature is often termed the *plasticity* of the epigenome.\(^{13} \)\(^{15} \)\(^{37} \)\(^{40} \) At the same time, it is increasingly recognised that some epigenetic variants are very stable over time and that they can be transmitted to daughter cells through mitosis or even to future generations through meiosis and embryogenesis. This phenomenon is often discussed as the *inheritance* of epigenetic variants.\(^{28} \)\(^{40} \)\(^{43} \) How is it possible to be dynamic and stable at the same time? And how may this apparent contradiction influence our perception and assignment of moral epigenetic responsibilities?

**Spectrum of plasticity**

Epigenetic mechanisms rely on a diversity of enzymes, such as histone acetyltransferases, histone deacetylases and DNA methyltransferases, which help create and break covalent
potentially inheritable modiﬁcative memory). In such tissues, even the most stable epigenetic some genes, in order to better respond to potentially recurring require a relatively fast process for the activation or silencing of.

The microenvironment in which these reactions are taking place can also signiﬁcantly inﬂuence an epigenetic variant’s level of plasticity. A very dense, and thus closed, tridimensional space (sterically hindered microenvironmentii) or surrounding electromagnetic forces may see their stability increase or decrease over time. Thus, the proximity of other epigenetic variants can modify the local microenvironment in a way that favours or impedes other epigenetic modiﬁcations. Consequently, the plasticity of epigenetic variants is known to vary depending on location.47

The spectrum of plasticity is space-dependent and also time-dependent. At different moments in cell growth and differentiation, some speciﬁc epigenetic modiﬁcations are more (or less) prone to occur. For instance, during embryogenesis and fetal development, epigenetic modiﬁcations occur at a very high rate and are responsible for the speciﬁcation of tissues and biological systems. From pluripotent embryonic stem cells to somatic cell lines, speciﬁc sets of genes are being silenced by DNA methylation, thus assigning tissues their speciﬁc functions within the organism.48

Windows of sensitivity, opportunity and sustainability
Epigenetics’ spectrum of plasticity adds further complexity to the already challenging task of assigning moral epigenetic responsibilities. To implement effective preventive and/or curative interventions based on evidence from epigenetics, it seems that we must consider some precise ‘windows of sensitivity’ that vary depending on multiple factors.44, p. 222 Moral epigenetic responsibilities should be recognised as necessarily context-dependent and relying on who has a capacity to act and also on the type of targeted chemical bond, its exact location in a speciﬁc tissue and its stage of development. Only then can we better identify windows of opportunity and the actors responsible for health interventions, thus satisfying Hedlund’s capacity criterion.

Once distinct biological systems are fully developed, their epigenomes’ plasticity varies, depending largely on their function. For instance, the immune and nervous systems, which are highly adaptive, also have very ﬂexible epigenomes. Periodically, they require a relatively fast process for the activation or silencing of some genes, in order to better respond to potentially recurring environmental stimuli in the future (e.g. immune memory, cognitive memory). In such tissues, even the most stable epigenetic modiﬁcations—consider, for instance, DNA methylation that is potentially inheritable—may undergo intraindividual variation during the life course.49 Thus, we should remember that different levels of plasticity of speciﬁc epigenetic variants correspond to different tissues and their stages of development, thus providing different opportunities for preventive and therapeutic interventions.

As windows of opportunity become widely recognised in the public arena, it may become increasingly unrealistic to advocate for the strictly prospective nature of epigenetic responsibility. Once opportunities for intervention become commonly known and prospective responsibilities are assigned to speciﬁc actors, will it still be reasonable not to hold them accountable retrospectively? For instance, if some chemical substance released by industry is proven to be epigenetically harmful, and regulations are implemented accordingly, would it not be justiﬁed to hold accountable a speciﬁc company? These questions are of importance for epigenetic responsibility, especially when the resulting deleterious epigenetic variant is programmed early in life, stable over time and hardly reversible by modifying lifestyle or living conditions.

In addition to considering when in the course of a lifetime a window of opportunity occurs, we should consider the length of exposure necessary for having a substantial effect on the epigenome. The precise biological process by which the environment gets progressively ‘imprinted’ in our genes is still unclear. It is important to consider the duration of the ‘exposure’ to newly changed conditions required to engage epigenetic mechanisms and substantially inﬂuence epigenetic memory.44, 30

For now, we can at least anticipate that the more stable an epigenetic variant, the more challenging it will be to reverse it—that is, it may require longer sustained exposure to a modiﬁed environment. On the one hand, histone acetylation and phosphorylation are mostly dynamic chemical reactions. Thus, they are easily reversible epigenetic modiﬁcations. Therefore, short-term variations in environmental stimuli may be sufﬁcient to reverse them. Simultaneously, such induced modiﬁcations’ high instability translates into potentially very brief duration. On the other hand, modifying DNA methylation patterns may require increased and sustained efforts, but their variation would normally last longer.45, 46, 48 Put simply, short and sparse events may often be insufﬁcient to impact long-term epigenetic health. Timeframes of exposure should be taken into consideration when implementing preventive and therapeutic solutions to epigenetic disorders.

Yet again, the tension between the plasticity and the stability of epigenetic variants informs us vis-à-vis important aspects of epigenetic mechanisms implicated in deﬁning and assigning epigenetic responsibility. Depending on the position of a targeted epigenetic variant on the spectrum of plasticity, the required sustainability of the health intervention to be implemented may also vary. To avoid only temporary beneﬁcial effects of future preventive health policies and medical treatments, discussions of epigenetic responsibility should include considerations of plasticity and sustainability.

Perspectives of distributive justice
Rothstein et al51 describe three important justice-related concerns that are highlighted by research in epigenetics: environmental justice, intergenerational equity and equitable access to healthcare. These areas differ importantly in their focus, regarding what should be distributed equitably, among whom, by whom and in what situation. Environmental justice focuses on geographically/spatially based inequalities, whereas intergenerational justice focuses on temporally based inequalities. Environmental justice focuses on the fair distribution of

Covariant bonds are relatively solid and thus stable chemical bonds that hold a high energy of activation. They usually require the recruitment of speciﬁc enzymes (catalyst proteins) to be formed or broken in human cells.

A sterically hindered microenvironment is hardly accessible for enzymes and chemical groups. Thus, when chromatin is sterically hindered at the locus of a speciﬁc gene, its transcription is impeded.


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preventive/public health interventions, whereas equity in access to healthcare focuses on the fair distribution of curative and palliative medical treatments. Thus, proper accounts of epigenetic responsibility should acknowledge possible tensions between these different aspects of distributive justice and the ethical consequences of their prioritisation.

It also becomes increasingly difficult to distinguish the types of epigenetic risk or disease that should be perceived as ‘fixed in nature’, from those that should be perceived as developing during the course of life and depending on other ‘non-biological factors’ such as personal motivation, familial and social support, available resources and infrastructures, or favourable institutions. As discussed by Loi et al58, the blurring of the boundary between ‘nature’ and ‘nurture’ may impact the core foundations of some theories of distributive justice, and to some extent, lead to the overlapping of the Rawlsian (social structural) and luck egalitarian views of equality of opportunity. Ultimately, this may add complexity to the already challenging task of defining interventions as prevention, treatment or enhancement strategies. It may also play a role in decisions as to which interventions should be publicly funded.

The recurring debate regarding whether health inequalities are in the domain of chance or choice is, we argue, central to the assignment of moral epigenetic responsibilities. For instance, in cases where the detected detrimental epigenetic variant was inherited due to parents’ lifestyle or living conditions—that is, when the epigenome is perceived as an ‘archive of prenatal environment’55, p. 526—it would arguably seem wrong to assign retrospective moral epigenetic responsibility to the affected individual. In contrast, if an epigenetic modification was known to have occurred due to unhealthy lifestyle choices (causation criterion), some may be convinced to assign retrospective moral epigenetic responsibility to the person, given she was informed of the risks (cognisance criterion) and of public health prescriptions against this behaviour (obligation criterion), and had control over these causes (capacity criterion). Hence, the public may be tempted to interpret epigenetic responsibility as a form of individual accountability for health.

However, such an interpretation would not stand up to ethical scrutiny from the point of view of the ‘option luck/brute luck’ distinction (Dworkin, luck egalitarianism). In an unequal society, even those individuals who are informed of the risk and have control over the causes may differ in relation to how informed they are and how much control they have. In some cases, people may choose to be less informed about and to have less control over epigenetic programming. Often, however, and especially in relation to social or natural disadvantages, how informed one is and how much control one has depends on circumstances outside of one’s control. In other words, fulfilling the cognisance and capacity criteria for being morally accountable for epigenetic harm to oneself or others would be a matter of brute luck.19

FURTHER LIMITATIONS TO NORMATIVE CLAIMS

Additional limitations of epigenetics should be taken into consideration when defining and attributing moral epigenetic responsibilities. Among these limitations we highlight three that have significant importance. First, we should be careful of potential misleading transpositions from animal studies to human biology. Animal models have suggested that maternal behaviour during pregnancy and after birth could impact the epigenetic programming of genes responsible for stress response and health later in the life of the offspring.35–38 Transposed to humans, such findings could lead to the identification of a set of ‘best practices’ a mother should adopt in order to promote the epigenetic health of her children. In response to such interpretations, Eric Juengst et al have rightly cautioned against ‘serving epigenetics before its time’55, p. 426—that is, against using mere murine models to draw premature conclusions regarding the duties of prospective human mothers.

Second, we should avoid drawing conclusions that take into account only partial information, that is, arbitrarily select certain findings and reject others. For instance, the role of mothers in the epigenetic programming of children was suggested in the scientific literature prior to that of fathers. Much attention has since been given to maternal behaviour during and after pregnancy. However, there is increasing evidence that the behaviour of fathers might also influence the epigenetic programming of offspring.60–61 Thus, it would be misguided to take into account only one part of the available evidence and distribute responsibilities in an unbalanced way, for example between women and men, for the well-being of children.

Third, we should be careful not to overestimate the transgenerational inheritance of epigenetic traits. We need to remember that the actual probability of an epigenetic variant being transferred across generations was proven to be significantly limited during embryogenesis by mechanisms largely ‘erasing’ the methylation patterns inherited from the maternal and paternal DNA brands.62–63 For this reason, it seems that the possibility of identifying and assigning intergenerational epigenetic responsibilities should be limited to only a few heritable epigenetic modifications around specific genes.

CONCLUSION

Epigenetics has recently been mobilised to promote certain ethically sensitive perspectives and political views. It is now of paramount importance for the bioethics community to address the ethical, legal and social issues that arise when moral epigenetic responsibilities are defined and assigned. In line with other commentators, we are concerned that some scholars, the public and the media are at risk of too hastily and simplistically assigning most epigenetic responsibilities to individuals (eg, parents, obese persons) without fully considering the ambiguous nature of epigenetic mechanisms. As was the case with genetics in the beginning of the 20th century, this could lead to prospective strategies that aim to coerce individuals into adopting healthy behaviours, as well as retrospective strategies that blame individuals for the unhealthy choices they have made in the past. As wisely anticipated by Gesche6:

Given the current climate of fiscal constraint, there might be an expectation that at risk individuals, who have the capacity to deal with epigenetic risk, but ignore their responsibility, could be found negligible and asked to substantially contribute to those health costs that reasonably can be assumed to have arisen from their negligence.6, p. 284

At the same time, opting for a simplistic conceptualisation of epigenetic responsibility as being prospective in order to prevent retrospective blaming, and belonging a priori to the State in order to prevent pressure on individuals, would misrepresent the complex nature of epigenetic mechanisms. We thus emphasise that progressing towards a comprehensive framework for an ethically sound assignment of moral epigenetic responsibility requires attention to scientific detail and limitations, as well as

19The authors wish to thank Dr. Michele Loi for alerting them to this specific point.
nuances in the philosophical foundations of distributive justice theories.

In this paper, we argued that it is oversimplistic to base the concept of epigenetic responsibility solely on existing biological distinctions between genetics and epigenetics. Such an approach may lead us to disregard important nuances, that we termed ‘biological ambiguities’, which are largely acknowledged within the research field of epigenetics itself, ambiguities regarding epi-
genetic normality and epigenetic plasticity. These two notions can have an important impact on the potentially burdensome assignment of moral responsibilities in line with recent scientific findings in epigenetics.

First, the concept of epigenetic normality should be further explored with regard to the complexity of the biological mechanisms behind epigenetic programming and inheritance, resulting for instance in the epigenome–environment mismatch model of disease development. As mentioned by Khan, we should acknowledge the ‘...difficulty of establishing thresholds for when epigenetic markers of risk can be considered injuries in the tort sense. It seems that one would first need to establish what a ‘normal’ risk profile is, which may not be possible’”, p. 284. We should also take into account differing sociocultural values and engage the public in this debate in order to best reflect the diversity of representations of an ‘ideal epigenome’. Differences in the ‘ideal’ among distinct populations may significantly influence the orientation of health interventions.

Second, taking into account considerable variation in the levels of epigenetic plasticity among variants is a prerequisite to assigning moral epigenetic responsibilities, since it is a necessary criterion for identifying the actual ‘capacity to act’ on epigenetic health by some specific actors in society (citizens, parents, healthcare professionals, scientists, public health agencies, corporations, governments or international organisations). Depending on the epigenetic variant and disease at stake, different actors might be assigned novel (or enhanced) moral responsibility. Moreover, some windows of opportunity for health interventions—as well as timeframes of exposure for efficient intervention—will be identified as a result of more precise knowledge of the engaged epigenetic mechanism. For these reasons, epigenetic responsibilities should not be assigned a priori to a single type of actor (eg, the individual or the State). Neither should we consider epigenetic responsibilities to be merely prospective. More options are possible and should not be excluded without debate. The bioethics discourse regarding epigenetic responsibility should be enriched by a sophisticated articulation of the ambiguous nature of epigenetics and nuanced theories of distributive justice that interface with our new understanding of nature and nurture.

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Extended essay
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