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Epigenetics and DOHaD: how translation to predictive testing will require a better public understanding

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Review

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Abstract

Epigenetics is likely to play a role in the mediation of the effects of genes and environment in risk for many non-communicable diseases (NCDs). The Developmental Origins of Health and Disease (DOHaD) theory presents unique opportunities regarding the possibility of early life interventions to alter the epigenetic makeup of an individual, thereby modifying their risk for a variety of NCDs. While it is important to determine how we can lower the risk of these NCDs, it is equally important to understand how the public's knowledge and opinion of DOHaD and epigenetic concepts may influence their willingness to undertake such interventions for themselves and their children. In this review, we provide an overview of epigenetics, DOHaD, NCDs, and the links between them. We explore the issues surrounding using epigenetics to identify those at increased risk of NCDs, including the concept of predictive testing of children. We also outline what is currently understood about the public's understanding and opinion of epigenetics, DOHaD, and their relation to NCDs. In doing so, we demonstrate that it is essential that future research explores the public's awareness and understanding of epigenetics and epigenetic concepts. This will provide much-needed information which will prepare health professionals for the introduction of epigenetic testing into future healthcare.

Introduction

Epigenetics describes the study of molecules and mechanisms that can perpetuate alternative gene activity states in the context of the same DNA sequence.[1] Epigenetic state is influenced by genes, environment and development. Current evidence implicates epigenetic mechanisms in mediating risk for many non-communicable diseases (NCDs): chronic, non-infectious conditions which collectively contribute to an increasing burden on the healthcare system as their prevalence increases. The Developmental Origins of Health and Disease (DOHaD) theory presents unique opportunities regarding the possibility of early life interventions to alter the epigenetic makeup of an individual, thereby modifying their risk for a variety of NCDs.[1] While it is important to determine how we can reduce the risk of NCDs, it is equally important to understand how the public's knowledge and opinion of DOHaD and epigenetic concepts may influence their willingness to undertake interventions for themselves and their children to prevent NCDs.

In this narrative review, we provide an overview of epigenetics, DOHaD, NCDs, and the links between them. We explore the issues surrounding the use of epigenetic testing to identify children and adults at increased risk of NCDs. We also outline what is currently understood about the public's understanding and opinion of concepts related to epigenetics and DOHaD, and their relationship with NCDs. In doing this, we demonstrate that it is essential that future research explores the public's views and understanding of epigenetics and epigenetic concepts, providing much needed information which will prepare the public and health professionals for the introduction of epigenetic testing into healthcare in the future.

Search strategy

Publications for this literature review were obtained through searches of the Medline and Embase databases, as well as Google Scholar and Discovery at the University of Melbourne, using combinations of the following and related search terms: 'epigenetics', 'genetics', 'attitudes to health', 'DOHaD', 'parents', 'opinions', and 'chronic health'.

Epigenetics

It is currently widely accepted that the developmental trajectory of an individual is not simply a competition between two opposing factors (nature and nurture), but rather represents a

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complex interaction between genetic and environmental factors.[2-4] Genetic (nature) and environmental (nurture) factors do not act independently of each other during development.[2] Instead, they interact in a number of different ways, one of these being through epigenetic mechanisms. Furthermore, this gene-environment interaction can change and evolve throughout a person's life,[3] suggesting that it is not only the initial developmental stages of life which influence an individual's health and risk of disease. Epigenetics has provided the means for a paradigm shift in the nature versus nurture debate.[5]

Conrad Waddington was the first to define epigenetics as 'the interactions of genes with their environment, which bring the phenotype into being' (p.298).[6] His idea was supported by the discovery of a potential underlying mechanism of epigenetic action, DNA methylation, in the 1970s by Holliday and Pugh.[6] The word 'epigenetics' has historically been ambiguous; its definition has changed dramatically over time as the science behind it has progressed.[7] Today, however, the term 'epigenetics' is generally used to describe more specifically modifications to DNA and gene expression that do not involve changes to the DNA sequence itself,[6-10] or alternatively, 'experience-dependent molecular alterations to DNA or to proteins that alter how genes behave without changing the information they contain' (p.171).[11]

Epigenetics plays a major role in mammals in phenomena such as genomic imprinting (where parent-of-origin epigenetic markers determine gene expression) and X-inactivation (the epigenetic process by which one X chromosome is deactivated in females).[6] Epigenetic markers (such as DNA methylation, histone modification, and DNA packaging) are involved in the regulation and expression of genes, both spatially (across different tissue types) and temporally (across developmental stages).[6,8] Epigenetic markers control gene expression by affecting when and how genes are expressed.[8] Epigenetic markers are unique compared to DNA sequence for a number of reasons, including their susceptibility to influence by the environment.[8] It is also plausible that in some cases, they may be transmissible from parent to offspring.[6] In order to understand the influence that the environment has on epigenetic markers, and their potential inheritance, it is important to first understand the process of epigenetic reprogramming.

Epigenetic reprogramming

Epigenetic reprogramming occurs at several time points during development, including gametogenesis (when eggs and sperm are created) and in early embryogenesis[6,12] (Fig. 1). Epigenetic reprogramming involves genome-wide 'resetting' of epigenetic markers,[6] the best understood of which is DNA methylation. Global demethylation is thought to occur in order to restore totipotency to the cell; however, some areas of the genome are protected from this global demethylation, such as imprinted genes.[6,13] Epigenetic markers within these regions are known as 'parent-of-origin methylation marks' (p.272)[12] and are essential for the correct expression of these genes. De novo methylation of the genome then occurs around the time of implantation, which coincides with the first cell lineage determination stage[6,13] and establishes a new pattern of DNA methylation in the blastocyst.[12] There are currently around 100 known imprinted genes; however, a growing consensus suggests there are likely other genes that also elude reprogramming through similar mechanisms.[14] This is the basis of intergenerational epigenetic inheritance.[8,13] Because of this global demethylation and subsequent de novo methylation process, there are several time points at which the epigenome is most sensitive to disruptors, namely during gestation, neonatal development, adolescence, and late adulthood. However, the epigenome is at its most vulnerable during embryogenesis,[6] gestation and newborn stages[8] due to high rates of cell division at these times. Furthermore, changes to epigenetic state can be sensitive and specific to the developmental stage at which they occur.[8]

Although intergenerational epigenetic inheritance has been observed in mammals,[6,14] the mechanism by which it occurs remains elusive.[15,16] Knowledge of mitotic inheritance of epigenetic markers is well established; however, the global demethylation and reprogramming which occurs during gametogenesis and after conception poses a challenge for understanding the intergenerational inheritance of epigenetic markers.[15] It should be remembered that although the following concepts are described mostly in terms of intrauterine environment, both maternal and paternal effects have been observed in transgenerational epigenetic inheritance,[10,12] hence, 'the paternal influence on epigenetic alterations in offspring should not be neglected' (p.274).[12]

Epigenetic exceptionalism

While there is much research focusing on the ethical issues of genetic concepts and genetic inheritance, there has been argument as to whether, ethically, epigenetics should be considered any differently.[8,17] From a scientific point of view, it is clear that the two have both similarities and differences. The most obvious difference between genetics and epigenetics is that, unlike genetic changes, epigenetic changes can be reversible.[8] Possibly less known is the fact that epigenetic changes occur more frequently than DNA mutations.[8] Furthermore, unlike genetic mutations, excluding the mechanism of mutagenesis, epigenetic markers may be influenced by the environment.[8,18] A similarity between genetics and epigenetics is that epigenetic changes may also be inherited.[8] Some have suggested that, despite its differences, epigenetics poses the same ethical issues as genetics, albeit potentially more complex.[8,18] However, because epigenetic variants can be reversible, and therefore more easily prevented or treated, responsibility on parents and societal blame for children's epigenetic conditions could be greater than that for genetic conditions.[4]

Developmental plasticity and developmental mismatch

Developmental plasticity, sometimes referred to as phenotypic plasticity,[3] biological embedding,[19] or fetal programming[20] is the process whereby a fetus 'utilizes environmental cues to adjust individual phenotype to the current and predicted environment' (p.8).[13] This allows the fetus to use information about the current environment as a 'weather forecast' for the future environment, and to develop and adapt accordingly.[19] The process of developmental plasticity not only explains how one genotype can produce a range of phenotypes,[6,21] but it also provides an evolutionary advantage. This is because developmental plasticity allows the fetus to become best adapted to the predicted environment by adjusting its phenotype to best match environmental demand.[3] Developmental plasticity is therefore thought to help an individual more quickly adapt to their environment, bypassing the long process of genetic evolution.[13,22]

Because of developmental plasticity, the environmental factors acting during an individual's early life set the trajectory for their developmental course, moulding the phenotype to those specific environmental inputs.[23] It has therefore been suggested that the early life environment can affect the phenotype permanently

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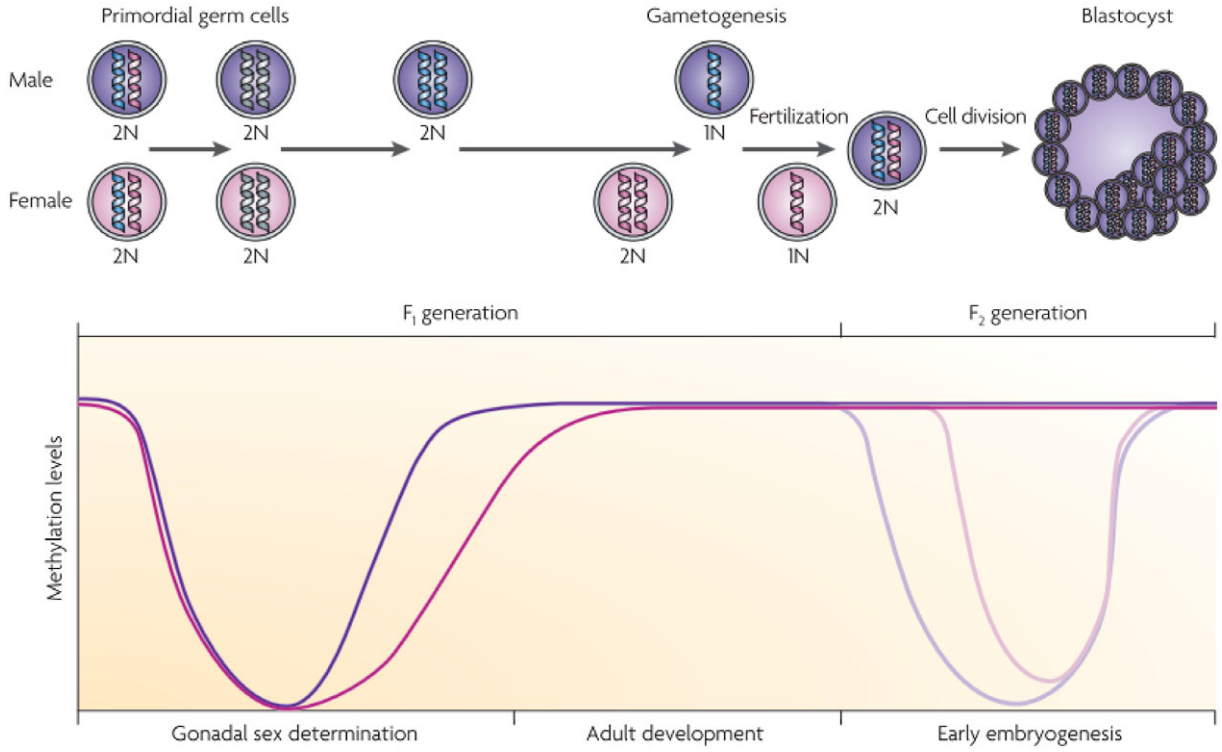


Fig. 1. Alterations in DNA methylation status during cell development. Reused with permission from Jirtle and Skinner[16]. Global demethylation (and therefore epigenetic reprogramming) occurs at two key time points during development, during gametogenesis and early embryogenesis.

and into adult life.[13] At the molecular level, the concept of developmental plasticity describes an individual's ability to 'tune' gene expression[13] through a 'weather forecast'[22] from the mother. This tuning can be achieved via epigenetic mechanisms. Epigenetic programming is therefore proposed as a mechanism for developmental plasticity,[3,4,6,12] as it affects regulation of gene expression, and is both influenced by early life environment, and consistent into adult life.[13]

Although epigenetics may have conferred a selective advantage throughout evolutionary history, today it instead exacerbates disease risk across generations.[13] The reason for this can be explained through the 'developmental mismatch' theory, where the future environment does not reflect that which was predicted, resulting in the individual being at increased risk of disease.[13] Although such adaptations may be beneficial in the short term, they may cause disease in the long term if the environment changes.[20] Such dramatic changes in predicted and actual environment can result from circumstances such as inaccurate environmental cues during gestation,[13] or dramatic shifts in nutrition due to improved socio-economic status. Godfrey *et al.*[13] also suggest that the degree of mismatch between the predicted and actual environment is directly related to the risk of disease. This is particularly relevant for societies undergoing rapid economic growth,[13] where one generation may experience a far richer environment than previous generations.

The developmental mismatch concept was shown most notably in a study conducted by Roseboom *et al.*,[24] who examined individuals who had been exposed to extreme famine in the Netherlands during World War II. Because the Dutch famine occurred over a short period of time (only a few months), records were kept immaculately, and the population were well-nourished both before and after the famine, this particular occurrence provided a unique opportunity to study the effects of undernutrition on pregnant women and their resulting children.[20,24] The study revealed that the undernutrition of mothers during pregnancy affected a child's health in later life,[24] and that the effect directly depended on both the timing during gestation at which the famine was experienced and on the specific systems under embryonic and fetal development at that time.[24] Outcomes such as adult body size, diabetes, and schizophrenia showed the most association with prenatal exposure to famine.[20] Epigenetic changes also showed an association with prenatal famine, providing a possible mechanism for the adult disease outcomes.[20]

Developmental Origins of Health and Disease

A major implication of the developmental plasticity and developmental mismatch concepts is the overarching DOHaD theory.[23] Sometimes referred to as the 'fetal basis of adult disease' or the 'early origins' theory, the DOHaD theory suggests that 'nutrition and other environmental factors during prenatal and early postnatal development influence developmental plasticity, thereby altering susceptibility to adult chronic diseases' (p.298).[6] In addition, the First 1000 Days concept builds on the DOHaD theory by suggesting that the first 1000 days of development (from conception until age two) are the most crucial in affecting future disease risk.[25] The concept of the First 1000 Days has been described in the literature based on recent evidence emphasising the importance of this early life stage.[19,25]

Because of its implication in many common diseases, it is well accepted that the DOHaD concept has worldwide public health implications,[13] as the fetal environment impacts the developmental trajectory, and therefore disease risk, of every child across the globe.[23] Additionally, environmental factors can affect multiple

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future generations through the inheritance of epigenetic markers, despite their continued lack of exposure to such factors,[6] further emphasising the importance of epigenetic concepts in global health strategy. Despite this recognised importance, translation of DOHaD knowledge into public health policy and guidelines has been limited.[26]

Epigenetics and NCD

Evidence suggests that epigenetics plays a significant role in disease susceptibility in adult life.[6] Changes in epigenetic regulation are associated with an increasing number of diseases, including but not limited to: type 2 diabetes,[5,12,13,16] cancer,[5,6,12,16] cardiovascular disease,[5,13,16] obesity,[5,12,13,16,18,25] and mental illness,[5,6,9,16] suggesting that the range of epigenetic influence across all aspects of human health is vast. There is widespread agreement that epigenetics plays a significant role in human health,[27-29] and new evidence is emerging regularly linking epigenetic changes to increasingly more aspects of human disease.[29]

Also known as chronic diseases, NCDs are non-infectious, long-lasting conditions which are caused by a combination of genetic and environmental factors.[30] They include cardiovascular disease, cancer, chronic respiratory disease, and diabetes.[30] The prevalence of NCDs across the globe is increasing,[13,31] generating a significant burden on global economies and worldwide health.[23] As of 2014, NCDs were more common worldwide than communicable diseases, a statistic which is likely only to worsen.[32] Particularly in Western countries, where they present one of the major health problems,[24] NCDs are the modern-day epidemic.[33] For example, the global prevalence of type 2 diabetes is expected to double by the year 2030, and the prevalence of cardiovascular disease is expected to increase by 35%.[31] NCDs cause 41 million deaths worldwide each year, contributing to 71% of global mortality, and accounting for over 80% of premature mortality.[34] Furthermore, 85% of these premature deaths occur in low- and middle-income countries,[34] indicating the impact of social and economic deprivation on these diseases. There is a significant amount of evidence to suggest that environmental factors acting during the early stages of life are contributing to this rising epidemic.[31] Therefore, because the majority of these deaths are preventable,[34] there is an important need for appropriate interventions.

Predictive epigenetic testing

Some have suggested that early identification of those at increased risk of NCDs may help encourage individuals to undertake preventative measures.[32] Epigenetics provides new opportunities for biomarkers which identify those at increased risk of NCDs.[32,35,36] In fact, potential epigenetic biomarkers predictive of future disease are already being discovered.[37] For example, Murray[38] showed that DNA methylation state at birth is predictive of cardiovascular disease in late childhood. Research has also shown that DNA methylation is also associated with prenatal alcohol consumption and tobacco use.[37] Furthermore, advances in the field of cancer include the adoption of DNA methylation screening to help predict the efficacy of certain drugs.[39] Of course, these kinds of discoveries require not only labour-intensive research, but often time-intensive longitudinal studies in order to determine causality, rather than simply correlation.[37] However, these epigenetic biomarkers allow for predictive epigenetic testing for an increasing number of health conditions. This will have many benefits, including the opportunity to further the prospect of personalised medicine in everyday health care by targeting those individuals who are at an increased risk, and providing early interventions to mitigate that risk.[18,29] In particular, inroads into personalised medicine will provide opportunities for therapies targeted to the individual's epigenome.[39,40] Godfrey *et al.*[13] suggest that continuing research into epigenetic mechanisms will allow development of potential interventions. The reversibility of epigenetic markers provides a particularly promising opportunity for treatment and prevention of epigenetic disease,[8,27,32] resulting in a push for the advent of new epigenetic therapies.[27]

While predictive epigenetic testing may provide information to inform early intervention,[32] it may not necessarily lead to positive behaviour change. The Health Belief Model suggests that there are multiple factors which influence people's health behaviours, including their perceived risk of disease.[41,42] Risk perception is therefore an important consideration in assessing the personal and clinical utility of both testing and public health messaging, however there is limited research in this area in the context of epigenetic testing.

Public understanding and opinion of epigenetics

While there has been some research in exploring the public's understanding of genetic and environmental susceptibility to disease, in line with the 'nature versus nurture' debate,[2,43] research in this area is lacking. Some suggest that the public views genetic factors as contributing only a small role to human disease and associated with only diseases which are viewed as severe or incurable.[2] This is contrary to other literature showing genetic susceptibility plays a role in a significant portion of human diseases which are generally considered to be caused by environmental factors, such as lung cancer caused by cigarette smoking, pesticide and lead toxicity, infectious diseases and the effects of certain drugs. In fact, the 'gene-environment interaction is fundamental to nearly all diseases' (p.27).[2] Despite this, the majority of people understand that both genetic and environmental factors contribute to an individual's overall health; however, people tend to treat these as discrete factors without interaction.[43] This is contradictory to what epigenetic research suggests. Condit showed that the public tend to view genetics 'through the lens of heredity' (p.1)[43] rather than by understanding the underpinning biological mechanisms by which inheritance operates. While there is limited data about the public's awareness and understanding of epigenetic concepts, epigenetics is highly prevalent throughout mainstream media, creating potential for widespread misconception and over-hype.[44] Ultimately, studies show that the public's understanding of common disease genetics is low,[45,46] suggesting that their knowledge of epigenetics is likely to be even more limited.

Testing in childhood

Because predictive epigenetic testing is likely to occur in early childhood in order for early interventions to be most effective, ethical issues arise which are similar to those relating to predictive genetic testing in children. There has been much professional discussion surrounding the ethical appropriateness of genetic testing in children.[47] There has also been some research exploring parents' views of this issue[45,48-50]; however, some have suggested that this research is insufficient to fully explore the attitudes of parents and health professionals towards the genetic testing of children.[49] The vast majority of consensus statements advise against genetic

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testing in children for adult-onset conditions for which there are no effective preventative measures available in childhood[47,48]; however this is often in opposition to parents' views. Campbell and Ross[48] suggest that the views of parents vary greatly with regard to wanting to know their children's genetic predispositions to adult conditions. Almost half of the sample surveyed by Shkedi-Rafid *et al.*[50] were of the opinion that parents should be able to test their children for adult-onset conditions, even when there was no treatment or preventative measures available. Similarly, a study led by Tarini found that greater than one-third of parents expressed interest in predictive genetic testing for their children for untreatable adult-onset diseases.[51] Tercyak *et al.*[45] showed that parents saw the benefits of genetic testing in childhood to outweigh the risks. These benefits included the knowledge of the predisposition itself, and the associated preparedness that this knowledge provided, both emotionally and practically.[45,50] This may be in part due to the assumption of parents that although there were no known effective interventions, they may still be able to utilise the information (such as changing their child's diet or being more open to new treatments when they become available).[50]

Anticipating parents' questions, reactions, and general knowledge about genetic testing is important in order to provide the best healthcare possible, and to facilitate effective informed decision making[45,50] by educating health professionals as to the motivations behind parents' requests.[51] Further research into this area may allow the discrepancies between public and professional opinion to become clearer, and the reasons behind such discrepancies to be addressed.[50] As summarised by Etchegary et al., 'optimal utilisation of any genetic testing depends on the knowledge and attitudes of the potential consumers of genetic tests and technologies' (p.354).[52] This will likely also be the case with epigenetic testing, by allowing health professionals to be better prepared for the implementation of such testing in childhood. However, ethical issues surrounding the use of predictive testing for children, as well as equity and access of testing, will need to be considered as epigenetic testing is adopted.

How knowledge of DOHaD concepts can improve health outcomes

While there have been limited attempts at knowledge translation of DOHaD concepts beyond the scientific community,[53] early research suggests that educational interventions can influence health outcomes.[23,54] An example which is relevant in the context of epigenetics is a study from Bay *et al.*,[23,54] where adolescents' knowledge of DOHaD concepts before and after an in-school educational intervention were examined, and it was found that both knowledge and health outcomes were improved immediately following the intervention,[23] and at 12 months' post-intervention.[54] The participants showed increased positive lifestyle and nutritional behaviours as well as a better understanding of the long-term and intergenerational impact of these behaviours.[23] The overall conclusion suggested that these types of interventions may be more effective in early life, in comparison to more traditional mid-life changes,[23] providing better health as well as economic outcomes. This increased knowledge also has the potential to be passed down to future generations, providing further benefit to the extended family.[23]

For the evidence supporting DOHaD to benefit society as a whole, it must be understood by the public so they can make decisions about its use.[55] Therefore, educational interventions such as the one used by Bay *et al.*[23] are likely to be an important step in the prevention of NCDs. These types of interventions have been suggested at the prenatal stage,[31,35] during childhood,[56] or during adolescence.[32,55] Alternatively, before and during pregnancy would be an optimal time to target women, as it is at this stage that they are most receptive to health advice for their future children.[24] Others have recommended that addressing the challenge of NCDs will require a life-course approach, with interventions targeted at many life stages.[35] Limited research into the knowledge translation of DOHaD concepts also points to the recommendation that interventions should be aimed at multiple generations simultaneously.[53]

While increased knowledge is likely to lead to improved overall health outcomes,[23] it is also important that we do not forget the large impact of socio-economic factors on NCD disease risk.[30] Being impoverished greatly increases an individual's risk of NCDs due to increased exposure to environmental factors such as tobacco use and poor diet.[30] Educational interventions that shed light on human behaviour and its impact on transgenerational epigenetic inheritance should be careful not to place blame and increase stigma on communities – and particularly mothers within these communities – affected by such socio-economic factors. Additionally, improved public awareness and understanding of epigenetics and DOHaD concepts should be just one intervention in a suite of public health initiatives designed to combat the increasing prevalence of NCDs globally, with a focus on disadvantaged populations with potentially less control over environmental factors impacting the health of future generations.

Conclusion

Research today is only beginning to delve into the possible consequences of epigenetic states in predicting disease risk with evidence currently too preliminary to provide recommendations for interventions. There is still much to be learnt about epigenetics and the DOHaD theory, and their respective effects on human health.[57] However, epigenetics is currently one of the most rapid growing fields of biology[40]; 'epigenetics is in vogue',[11] suggesting that it will not be long before epigenetic links between environment and disease are numerous and replicated, and epigenetic testing becomes easily accessible to the average consumer. In preparation for such a time, we must better grasp the public's awareness and understanding of epigenetics, DOHaD, and their link to NCDs. This will better ready the health system to tackle this novel form of risk information which is likely to be generated from epigenetic testing.

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