

## Studying Vulnerable Populations Through an Epigenetics Lens: Proceed with Caution

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[See table of contents](#)

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### Article abstract

Epigenetics – the study of mechanisms that influence and modify gene expression – is providing unique insights into how an individual's social and physical environment impact the body at a molecular level, particularly in populations that experience stigmatization and trauma. Researchers are employing epigenetic studies to illuminate how epigenetic modifications lead to imbalances in health outcomes for vulnerable populations. However, the investigation of factors that render a population epigenetically vulnerable present particular ethical and methodological challenges. Here we are concerned with demonstrating how, in targeting certain populations for epigenetic research, this research may be pathologizing socio-cultural and medical practices in those populations in a way that *increases* their vulnerability. Using a case study approach, this article examines three vulnerable populations currently of interest to epigenetic researchers – Indigenous, autistic, and transgender populations – in order to highlight some of the challenges of conducting non-stigmatizing research in epigenetics.

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ARTICLE (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

## Studying Vulnerable Populations Through an Epigenetics Lens: Proceed with Caution

Katie Saulnier<sup>a</sup>, Alison Berner<sup>b,c</sup>, Stamatina Liosi<sup>d</sup>, Brian Earp<sup>e</sup>, Courtney Berrios<sup>f</sup>, Stephanie O.M. Dyke<sup>g</sup>, Charles Dupras<sup>h</sup>, Yann Joly<sup>i</sup>

### Résumé

L'épigénétique – l'étude des mécanismes qui influencent et modifient l'expression des gènes – fournit des informations uniques sur la façon dont l'environnement social et physique d'un individu a un impact sur le corps au niveau moléculaire, en particulier dans les populations victimes de stigmatisation et de traumatismes. Les chercheurs ont recours à des études épigénétiques pour comprendre comment les modifications épigénétiques entraînent des déséquilibres dans les résultats de santé des populations vulnérables. Cependant, l'étude des facteurs qui rendent une population épigénétiquement vulnérable présente des défis éthiques et méthodologiques particuliers. Nous nous attachons ici à démontrer comment, en ciblant certaines populations pour la recherche épigénétique, cette recherche peut pathologiser les pratiques socioculturelles et médicales de ces populations d'une manière qui accroît leur vulnérabilité. En utilisant une approche d'étude de cas, cet article examine trois populations vulnérables qui intéressent actuellement les chercheurs en épigénétique – les populations autochtones, autistes et transgenres – afin de mettre en évidence certains des défis à relever pour mener une recherche non stigmatisante en épigénétique.

### Mots-clés

épigénétique, éthique de la recherche, confidentialité, vie privée, recherche en sciences sociales, populations vulnérables

### Abstract

Epigenetics – the study of mechanisms that influence and modify gene expression – is providing unique insights into how an individual's social and physical environment impact the body at a molecular level, particularly in populations that experience stigmatization and trauma. Researchers are employing epigenetic studies to illuminate how epigenetic modifications lead to imbalances in health outcomes for vulnerable populations. However, the investigation of factors that render a population epigenetically vulnerable present particular ethical and methodological challenges. Here we are concerned with demonstrating how, in targeting certain populations for epigenetic research, this research may be pathologizing socio-cultural and medical practices in those populations in a way that *increases* their vulnerability. Using a case study approach, this article examines three vulnerable populations currently of interest to epigenetic researchers – Indigenous, autistic, and transgender populations – in order to highlight some of the challenges of conducting non-stigmatizing research in epigenetics.

### Keywords

epigenetics, research ethics, confidentiality, privacy, social science research, vulnerable populations

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## INTRODUCTION

The modern field of epigenetics – the study of mechanisms that influence and modify gene expression – is giving researchers unique insights into how an individual's social, cultural, and physical environment affect the body at a molecular level (1). In part because these modifications show the potential to be both heritable and reversible, this finding has raised a great deal of interest for researchers engaging with populations who are considered vulnerable by way of their environmental and social exposures. In particular, researchers are employing epigenetic studies to illuminate how epigenetic modifications may lead to imbalances in health outcomes. Framing their research around these vulnerabilities, however, carries the risk of exposing these populations to increased levels of stigmatization and harm. The ethics literature on research with vulnerable populations typically focuses on two areas: the ability to consent to research, and exacerbated power imbalances between researchers and participants, such as those experienced by groups who have historically been the targets of unethical research practices (2). While both concerns exist as well for epigenetics research, the close link between a group's status as vulnerable and the investigation of vulnerability as a *target* of research intensifies many ethical and methodological challenges. In this article, we will therefore highlight ways in which conducting research framed around epigenetic "harm" may itself harm vulnerable populations by increasing stigmatization and pathologization.

## Vulnerable Populations & Epigenetics

The phrase "vulnerable population" carries multiple meanings within the research context. In research ethics policies and guidance documents, "vulnerable" often refers to individuals with limited decision-making capacity or power (3). This lack of

power is deeply entangled with experiences of discrimination, stigmatization, and exclusionary practices within the medical and research contexts and elsewhere that in turn generate other forms of vulnerability. For example, ethnocultural minorities who have historically been the targets of unethical research practices may in turn end up further excluded from research advances, notably by self-selecting out of research due to concerns about research conduct or historical trauma, exhaustion from being over-targeted for research recruitment, paternalistic ethical and legal regulations, or due to gaps in recruitment practices. In other areas, the lack of decision-making power that is attributed to individuals with cognitive disabilities may in turn exacerbate power imbalances between researchers, caregivers, and research participants. These definitions more recently expanded to incorporate an intersectional understanding of vulnerability that unpacks the challenges of working with multiply marginalized individuals (4). Finally, current experiences during the global coronavirus pandemic are bringing new attention and perspectives to the conversation around vulnerability, reiterating vulnerability not as a fixed state, but as something that may be intensified or alleviated for different individuals and groups through changing policies and circumstances (5).

Populations of interest to epigenetic researchers may be considered vulnerable by virtue of different factors, including discrimination and stigmatization, lack of access to healthcare and healthcare information, and questions about capacity for free, full and informed consent (1). A great deal of research already exists on strategies to mitigate these harms and to encourage participation from excluded groups in new research, much of which is applicable to epigenetics research (6). Other challenges, however, may require new types of strategies and methodologies. Because epigenetics enables us to examine the social and environmental contributors to health and disease at a molecular level, populations that have experienced large-scale trauma or early-life adversity are being examined to provide evidence of the patterns already noted by researchers in other medical and social science fields. In providing a new layer of evidence for existing observations of health precarity and reduced health outcomes for populations that face discrimination, stigmatization, and trauma, researchers risk reifying stereotypes and placing contestable normative values on cultural behaviours or cognitive differences.

Here, we will examine the ways in which epigenetic research, in seeking to confirm epidemiological observations concerning behaviors and practices at the molecular level, risks contributing to stigmatization. Because epigenetics research ties together the biological and the social, the potential for increased pathologization – the presumptively inappropriate or unwarranted treatment of a physical or behavioural state as though it were a medical condition – of socio-cultural practices will be particularly high (7). There is also an increased potential for placing disproportionate personal responsibility for health on already vulnerable populations. Moreover, research that seeks epigenetic links amidst very broad groups that are considered vulnerable run the risk of homogenising those same groups and failing to undertake an intersectional analysis of the many varying factors that might influence the marginalization or vulnerability of a given member of that wider community (4). Finally, although the language of vulnerability is used here to indicate groups that have been harmed or are at risk of harm in the research context, this terminology belies the extreme resiliency that individuals and communities have shown in the face of these and other harms. The language of epigenetic “harm” in particular works to pathologize the bodies of those deemed vulnerable, frequently by researchers external to that identity, and precludes us from seeing how an individual or community might be viewed instead as having developed epigenetic *reinforcement* as a result of those experiences.

A note: we have used the term “social” throughout this paper largely to refer to the broad collection of experiences, practices, and environments through and in which people may encounter epigenetic modifiers. When the term “cultural” is used in place of or in addition to social, it is to refer more specifically to those experiences, practices and environments that are most personally relevant to the individual or the community with which they identify. Nevertheless, the delineation between these two terms is not always clear; nor is there a clear line between the socio-cultural environment and the biological factors that arise from it. This complexity should be noted as a further confounding factor in epigenetic research that looks to tie these domains together.

## Materials and Methods

Using a case study approach, this article will examine three vulnerable populations currently of interest to epigenetic researchers – Indigenous, autistic, and transgender populations – and use these as examples to highlight some of the challenges of conducting non-stigmatizing research in epigenetics. The populations were selected because they represent a diversity of vulnerable populations – ethno-cultural, neurodevelopmental, and social – where epigenetics researchers have shown particular interest in understanding those vulnerabilities. Moreover, they provide us with examples of research into the relationship of the social, environmental and biological factors for health outcomes at different stages, ranging from a significant amount of existing scholarship (Indigenous populations) to research that is just emerging (transgender populations). We then examine the commonalities between these cases and propose several points to consider in conducting studies with populations whose vulnerability may be increased by their involvement in epigenetic research.

## INDIGENOUS POPULATIONS

### Epigenetics, Health, and Research

Indigenous communities<sup>1</sup> have emerged as populations of particular interest to epigenetics researchers in large part because of the clear examples of intergenerational trauma, including collective intergenerational trauma (8). Other populations that have faced large-scale trauma – notably Holocaust survivors (9), survivors of the Dutch Famine (10), and African American populations (11) – have been similarly targeted by epigenetics researchers seeking to understand both the effects of trauma on the body, and their potential heritability. Researchers with an interest in the developmental origins of health and disease (DOHaD) – a field which examines how early life (at or prior to conception, in utero, and infancy and early childhood) environments impact health and disease risk – have been particularly interested in using epigenetics, because it presents a promising new path for understanding trauma and associated health disparities. Notwithstanding the interest in this topic, thus far this work has been largely theoretical in nature; a clear epigenetic link is posited because of the increasing understanding of the impacts of trauma on the epigenome, but empirical research is still in its early stages.

Health disparities amongst Indigenous populations include cardiometabolic disease risk, type 2 diabetes, life expectancy, and vulnerability to the development of psychiatric disorders<sup>2</sup> (12). Indigenous women and children in particular experience profound health disparities worldwide (12). Although many aspects of these disparities are tied directly to the *current* harms of colonialism (e.g., lack of access to necessary services, stress of the lived experience of racism, loss of cultural and traditional ways of life), the potential heritability of epigenetic effects shown in early animal studies suggests that even trauma experienced by one's parents and grandparents may have a tangible effect at the molecular level (1). While the effects of colonization on population health have been previously well-documented in epidemiological studies, it has been suggested that epigenetics research may help to separate the socio-cultural effects from the biological. Research with other racialized and marginalized populations suggests that the experience of racism itself may produce epigenetic effects on the body (13). Caution is necessary, however, in separating out the correlation between behaviour or experiences and epigenetic markers. As previous ethical, legal and social issues (ELSI) research in epigenetics has noted, studies that seek to link the social environment of marginalized populations to epigenetic outcomes can in turn cause harm by pathologizing the environment itself, alongside accompanying social and cultural activities (1,7).

The history of research in Indigenous spaces has been marked by harm, and genetics research in particular has replicated colonial violence through improper, incomplete, or invalid consent; unethical use of material gathered; and an unwillingness to return useful research results to participating or enlisted communities. For example, in British Columbia, Canada, researchers collected DNA samples from the Nuu-chah-nulth in order to conduct research on high levels of rheumatoid arthritis present in this Indigenous population. When no genetic link was uncovered, the researchers used the samples in a number of other unconsented studies, including those on intravenous drug use (14). Similarly, in Arizona researchers collected samples from the Havasupai Tribe for diabetes research, then used the information without consent for sensitive studies, including those on migration patterns and on schizophrenia (15). In Canada, some of the trauma outcomes under investigation were first perpetuated in the name of scientific experimentation; in the 1940s and 1950s, the Canadian government used widespread malnutrition in Northern Manitoba Indigenous communities to test nutritional supplements, leaving a control group in starvation (16). Another group of researchers performed experiments on children in residential schools, withholding milk, vitamin C supplements, iron-fortified bread, and preventive dental care in order to examine the effects of deprivation (17).

With 370 million Indigenous persons worldwide in approximately 90 countries, there is clearly no single approach to health research or health promotion that will apply universally (18). Nevertheless, it is true that the medical impacts of colonialization on Indigenous populations are astronomical in scope of harm.<sup>3</sup> Much of this harm stems from the social and economic impacts of genocide; cultural eradication has led to multi-generational “psychological, physical, and structural disadvantages” that manifest at the cellular level (19). Colonialism functions as an “ongoing structure of domination”, including interference via invasive research and suppression of traditional medicine, food, and ways of living (20). This is compounded by factors such as rural location, communication challenges, and socio-economic status, which create barriers to accessing healthcare (21).

The ongoing nature of colonialism makes it very challenging to untangle causation of harm; non-Indigenous researchers are only now beginning to recognize and acknowledge the full scope of the situation. Over the last decade, researchers have undertaken research into the direct epigenetic link between intergenerational trauma and health disparities, including the epigenetic effects of malnutrition, psychosocial stress, and environmental toxicant exposures, making research with Indigenous communities one of the clearest examples of studies of inherited epigenetic effects of trauma in humans (19). While much of the interest in Indigenous epigenetics research stems from the ability to track intergenerational historical trauma, it must also be recognized that violence and discrimination continue to exacerbate health risk factors; for instance, at any given time there are more than 100 drinking water advisories on First Nations reserves across Canada (22).

<sup>1</sup> The term “Indigenous communities” is extremely broad, and the health and socio-cultural considerations for different communities will vary enormously; here, we highlight just some of the research that has been framed as “Indigenous” epigenetic research.

<sup>2</sup> “Obesity” is frequently included in the list of health disparities facing Indigenous populations. However, the classification of weight as a disease is considered controversial amongst critical theorists and a growing number of health researchers, in part due to increasing evidence that the association between weight and negative health outcomes has been overstated in the scientific literature, to the detriment of the health of individuals whose BMI classifies them into this category. As such, we have excluded obesity from our list, but do note that it is another factor considered by researchers.

<sup>3</sup> For a more comprehensive look at the widespread violent impact of colonialization in Canada, see the Truth and Reconciliation Commission of Canada's [Truth and Reconciliation Report](#), as well as the report on [Missing and Murdered Indigenous Women and Girls](#).

## Ethical and Legal Considerations

Research conducted with Indigenous populations, particularly research conducted by non-Indigenous researchers, is inherently fraught, not only because Indigenous populations represent a uniquely vulnerable population, but because that vulnerability in the medical context has been both generated and reinforced by scientifically and morally flawed research practices and approaches to healthcare delivery (15). Concerns around epigenetics research in Indigenous populations more specifically show that the epigenetics context intensifies and complicates existing bioethical concerns (19). In particular, by conducting research into epigenetic harms that are themselves the result of state-sanctioned violence, researchers continue to harm Indigenous communities in the name of science, perpetuating a cycle of trauma.

Epigenetics research in Indigenous populations also exacerbates concerns around the harms raised by stereotyping in medical research; by classifying Indigenous peoples as epigenetically harmed, there is a risk that the group will come to be perceived by others as somehow biologically “damaged”. As Warin notes, “the shaping of the right to protection from biosocial injury is potentially empowering but also has the capacity to conceal forms of governance through claimants’ identification as “damaged,” thus furthering State justification of biopolitical intervention in Indigenous lives” (19). In particular, scholars have expressed concerns that epigenetics researchers risk reifying a biological conception of race and pathologizing cultural practices (7).

It is unclear if existing guidance on research with Indigenous Peoples is sufficient to fully address these concerns. The legal and policy work addressing research ethics with Indigenous populations has primarily focused on issues of informed and culturally appropriate consent to research. Epigenetics research, in engaging conversations about both genetics and behaviour/environment, requires particular attention regarding informed consent. While policy documents do not necessarily carry legal weight, they do set the tone for how research is to be conducted and non-compliance may give rise to important penalties, such as removal of funding. For example, Canada’s *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (3), adherence to which is a pre-requisite for receiving federal research funding for research with human participants, contains a separate chapter on research involving the First Nations, Inuit and Métis Peoples of Canada. Notably, researchers are required to view ethical considerations through the appropriate Indigenous lens, in addition to involving communities in research planning and approval and prioritizing Indigenous-led research initiatives. Similarly, in New Zealand, the *Te Ara Tika Guidelines for Māori Research Ethics: A Framework for Researchers and Ethics Committee Members* outlines a framework for addressing Māori ethical issues, with a focus on including Māori individuals throughout research ethics decision-making processes (23). In Australia, the *Australian Institute of Aboriginal and Torres Strait Islander Studies Act 1989* outlines the ethics framework for Indigenous research and is underpinned by the Guidelines for Ethical Research in Australian Indigenous Studies. These and other documents highlight the importance of inclusion of Indigenous peoples at all stages of the research process, and the need to develop effective and culturally appropriate consent mechanisms (18).

## AUTISTIC POPULATIONS

### Epigenetics, Health, and Research Context

Another population of interest to epigenetics researchers are autistic individuals<sup>4</sup>. The current medical model of autism describes it as a neurodevelopmental condition featuring impairments in social interactions, communication, and restrictive behaviour patterns. Advocates of the neurodiversity movement, by contrast, describe autism as a natural human variation with its own combination of strengths and challenges (24). The breadth of experiences and traits associated with autism creates a significant challenge for any research that seeks to discover a singular marker as being associated with autism. Research that has aimed to paint the autistic experience with one brush has typically failed to do so without missing out on significant parts of the population, while simultaneously pathologizing the parts that it manages to capture.

In part for this reason, research ethics in the autistic context has long been fraught with problems. Historically, researchers have focused on the pathologization of maternal environmental influences in autism in harmful ways, particularly through the now-debunked theory of “refrigerator mothers” (e.g., cold and non-nurturing mothers) as the cause of autism (25). Bioethicists have already raised concerns that epigenetics research presents analogous issues in its focus on animal models and maternal influence (1); given this history, epigenetics research that focuses on maternal exposures as the locus of autism development and that ignores the potential role of paternal exposures may raise similar and repeated concerns around pathologization and sexism. Finally, gender and racial bias in autism research has resulted in widespread underdiagnosis outside the context of white men (26).

In general, research seeking to pinpoint a singular root environmental or biological cause of autism has come up empty, and researchers have seen potential for epigenetics to bridge these complex factors. Research into the epigenetics of autism is relatively advanced; however, theoretical frameworks underpinning epigenetics autism research show a murkier path than the correlation between Indigenous experience and trauma. While studies have shown high heritability, and a large volume of genetic studies with increasing sample sizes have identified numerous candidate genes, none have demonstrated large effect sizes (27). At the same time, several epidemiological studies have found associations between prenatal exposures, including stress and various infections, to the development of autism (28). Meanwhile, it is known that neurodevelopment, particularly

<sup>4</sup> There is debate within the use of identity-first language, “Autistic individuals”, or person-first language, “individuals with autism”. We here use the identity-first language preferred by many advocates within the autism community and neurodiversity movement, including one of our authors.

during the prenatal period, is tightly controlled through patterns of gene expression. This makes the neurodevelopmental process susceptible to epigenetic modifications affecting gene regulation and provides a potential mechanism by which environmental exposures could have an influence on the development of autism. Indeed, studies identifying differences in gene expression in post-mortem samples between brains of autistic and non-autistic individuals further suggest a potential role for epigenetics (28). Based on this potential, research has begun to confirm a role of epigenetics in autism. However, in the face of ableism and a history of excluding autistic individuals from decisions about research, there are concerns that causative research will be used (or instrumentalized) to diminish or eliminate the autistic community.

With regard to health concerns faced by autistic individuals, there are a number of medical and mental health conditions associated with autism, although it can be difficult to separate whether they share a biological basis with autism or are the result of unjust social forces such as insidious discrimination or other forms of mistreatment (29). Epilepsy, sleep difficulties, and gastrointestinal issues such as irritable bowel syndrome and gluten-intolerance are health issues that affect quality of life for many autistic individuals, in addition to broad autoimmune diseases. Anxiety and depression, which are also frequently co-diagnosed with autism, may stem from similar causal factors, or may be the result of stigmatization and discrimination. Finally, schizophrenic disorders, obsessive-compulsive disorder, bipolar disorder, and attention-deficit disorders also appear frequently in autistic individuals and are themselves stigmatized conditions (29). Autism advocates have expressed concern that the focus on the causal roots of autism, rather than on these health concerns, has ignored the priorities and needs of the autism community, including the treatment of these associated conditions (30). Additionally, in tying specific exposures in the mother pre-conception and during pregnancy to autism, epigenetic research risks exacerbating rhetoric that overburdens mothers with “responsibility” for their children’s autism (in the same vein as the “refrigerator mother” rhetoric), while simultaneously reinforcing the medical model idea that autism is an undesirable outcome, rather the social/neurodivergence perspective of autism as a difference.

## Ethical and Legal Considerations

Health researchers working in the field of autism research have typically examined two broad categories of questions: 1) what are the causes of autism, and 2) what are the health concerns faced by autistic individuals? The first of these questions is considered significantly more controversial than the second, as it raises concerns amongst autistic individuals that causal research will be used as part of cure/prevention paradigm, leading to prenatal tests or treatments that could be used to diminish the autistic population (31). Existing therapies that are employed with autistic children aimed at reducing the appearance of overt autistic behaviours, such as applied behavioural therapy, have faced intense criticism from within the neurodiversity movement for focusing on creating more compliant, rather than healthier and happier, autistic individuals (29). As such, genetic and epigenetic research that seeks to examine the root causes of autism have been met with skepticism and concern.

Legal protections for autistic individuals are generally subsumed under larger categories of laws protecting against discrimination on the basis of disability. For instance, the United Nations’ *Convention on the Rights of Persons with Disabilities*, of which 163 countries are signatories, includes commitments that researchers will not require disabled individuals to be disproportionately burdened by research risks, and addresses concerns broadly related to underrepresentation of disabled individuals in health research. Legislation surrounding autism specifically has not necessarily focused on the protection of autistic individuals directly involved in research or clinical contexts, but rather on plans for raising awareness of autism and access to treatments, or on the use of medical insurance to fund these treatments (32).

One concern in autism research has long been the distribution of research funding, where past studies have shown that funding for autism has been largely distributed to researchers in the fields of nervous system studies and genetics, to the exclusion of other important research on psychosocial well-being and non-medical care (33). As epigenetics autism research grows, more attention may be drawn from these other necessary forms of research and care, refocusing attention on the science of causality and cure. Finally, attention must be paid to the history of autism researchers’ focus on the appearance of autism in men and boys, which has resulted in an underdiagnosis of autistic women and girls (as well as transgender and non-binary children, who are disproportionately represented in autistic populations) (33). As we will see below, sex and gender differences in epigenetics research raise challenges of their own.

## TRANSGENDER POPULATIONS

### Epigenetics, Health, and Research Context

“Transgender” is a broad designation belonging to people who have physical, psychosocial, or behavioural characteristics relating to sex or gender that do not conform to socially dominant expectations. More narrowly, the term refers to those whose gender identity, that is, their strongly felt sense of themselves across a spectrum of gender experiences and expressions (e.g., boy/man, girl/woman, non-binary person, etc.) (34) is inconsistent with the gender category that is normatively associated with their birth-assigned sex, the latter being typically inferred from visible sex characteristics and based on a binary understanding (i.e., male/female) (35). Individuals whose gender identity corresponds with their natal sex categorization are referred to as “cisgender” (35). The term “transgender” was not coined until 1971; however, the existence of individuals who would likely be characterized as transgender today, as well as the presence of hostile prejudicial attitudes toward them, often resulting in harassment and discrimination, are present across human history.

Many, yet not all, transgender persons experience *gender dysphoria*. Gender dysphoria refers to the discomfort or distress associated with, or caused by, the felt discrepancy between gender identity and physical sex-typed traits or categorization, and this can be experienced in many different ways and to different degrees, including with respect to certain aspects of one's body or to the gendered social role expectations associated with their assigned sex (36). The presence of dysphoria is often used as a metric for determining access to gender-affirming care, despite not being a universally experienced by transgender individuals (34).

In the context of science and medicine, early studies classed the feelings or behaviours of transgender individuals as normatively "deviant" and focused on attempts to "cure" their perceived psychiatric illness; the recent backlash against the emergence of transgender rights has re-ignited and re-intensified this rhetoric. Accordingly, there has long been inappropriate and harmful treatment of the transgender population, both in clinical and research practices (37). Such treatment can occur in the course of general medical care, including the refusals of necessary medical services and the use of disrespectful identity-based language (e.g., misgendering), or in the course of transgender-specific care, for example, involving hormones or surgery. In the research context, the proportion of participation of the transgender population, compared to the general population, remains low (38). This may be the result of a) deliberate exclusion by researchers in their sample, possibly due to their impression that cisgender individuals will provide fewer confounding factors, or b) "self-exclusion", deriving from, among other factors, a lack of trust in the medical establishment based on experiences of transphobia.<sup>5</sup> Research with transgender adolescents has been especially exploitative; a prime example is a well-known 1993 study assessing the physical attractiveness of pre-adolescent transgender girls, framed in the paper as boys with gender identity disorder (39).

Compared to the autistic community discussed above, there is relatively little epigenetic research currently being conducted with transgender participants. Nor, as is in the case of Indigenous populations, has there been as widespread enthusiasm for this research as it pertains to health. However, the questions raised in research in general suggest that epigenetics research with transgender populations will likely emerge in the near future. Current epigenetic research on transgender populations falls into two main categories: first, research on the potential epigenetic *origins* of gender identity variance, and second, research on the possible epigenetic *consequences* of transitioning, with a particular focus on the effects of so-called cross-sex hormones. The etiology of gender dysphoria and gender identity variance is not fully known, although most researchers in the field point to a combination of social and biological factors. For instance, according to Theisen et al. (40), recent research has indicated that certain rare gene variants might be associated with sexually dimorphic brain development, which could contribute to gender dysphoria. Given this combination of social and biological factors, as well as the reliance of sex development – and, on some views, certain aspects of gender identity-development – on multiple levels of transcriptional control of DNA, epigenetics research in gender identity has emerged as a field of particular interest. Transcriptional control of DNA is partly governed by epigenetics, as well as by the differing exposures to potential epigenetic modifiers of sex and gender. Thus far, much of the work examining how epigenetic modifiers impact sex development has been conducted in animal models, limiting its usefulness in understanding human sex, much less gender identity. Moreover, medical practice with transgender individuals has trended and, in many cases, continues to trend toward pathologization and research that seeks to forcibly change gender identity. As such, this work is treated with concern by the transgender community, as it is unclear how research that seeks to examine the causes of gender variance would be harnessed to improve the lives of the population being studied.

Secondly, epigenetic research on transgender populations is examining the possible epigenetic consequences of transition, with a particular focus on the effects of cross-sex hormones (i.e., methylation of the oestrogen receptor following oestradiol treatment). "Transitioning" refers to the process by which an individual changes their gender presentation from the one associated with their assigned sex at birth to another gender expression (36). When transgender individuals transition, they are often embarking on changes aiming at lessening dysphoria caused by the incongruence between their gender identity, their physical appearance, and their treatment in society. As each of these factors differ for individuals, so too will their transition and the age at which they choose to embark on it (41). This may mean starting to wear or use gendered clothes or products that are socially associated with their gender identity. They may also be more likely to engage in behaviours or other activities that are expected to signal the gender by which they wish to be recognized by others. Further, they may choose to take so-called "feminising" or "masculinising" hormones. These typically include oestrogen, testosterone and gonadotrophin hormone analogues, which block the release of LH and FSH from the pituitary, as well as downstream release of oestrogen and testosterone. Finally, they may undertake surgical procedures to further align their bodies with their gender identity. While this research has thus far focused primarily on the epigenetic effects of hormonal transition, recent research suggests that some factors that accompany gender identity and expression can affect the epigenome due to differing environmental exposures, such as chemical properties in cosmetic makeup, or gendered behavioural differences in substance consumption (42).

Finally, although it is not an experience specific only to transgender individuals, high levels of stress and adversity, like those faced due to gender-based violence and discrimination, carry additional epigenetic implications. Stress and trauma early in life are particularly relevant in transgender populations; a recent study in the United States found that transgender and genderqueer adolescents report polyvictimization – the experience of multiple forms of abuse – at significantly higher rates than their cisgender counterparts (43). Early life stress has been shown to act as an epigenetic modifier in human tissues. Cicchetti and colleagues (44) used saliva samples from children who either had or had not suffered from certain adverse childhood events, e.g., physical or emotional abuse, in order to show differential methylation in genes associated with major

<sup>5</sup> Many, although not all, of these concerns are shared amongst the intersex population, i.e., individuals who do not fit into a binary sex categorization at any number of levels, including chromosomal, hormonal, or genital. However, for the purposes of this case study, we are specifically focusing on transgender vulnerability in epigenetic research.

illness, including cancer, cardiovascular disease and psychiatric disorder. This difference in life exposure has been postulated to have enduring effects. However, caution is needed in attributing the epigenetics effects of these stressors to epigenetic markers carried by transgender individuals; this experience of victimization and abuse is not an intrinsic or inevitable mark that appears on the transgender body, but rather, a consequence of stigmatization and violence.

## Ethical and Legal Considerations

While epigenetic research has the potential to highlight specific healthcare needs, it also has the potential to create or enhance certain vulnerabilities. First, it may increase existing social stigma that has accompanied the historical classification of gender variance as a physical or psychological illness. The inclusion of gender dysphoria in the DSM-V, the manual for diagnosis of psychiatric disorders, as well as the reliance on the presence of gender dysphoria as a gatekeeping measure for access to hormones and surgeries, is widely condemned within the transgender community as dehumanizing and stigmatizing (45). Instead, an approach may be taken that recognizes gender incongruence as being related to sexual health, but in a non-pathologizing way, in line with its classification in the *International Statistical Classification of Diseases and Related Health Problems*. The investigation of these potentially “causal” epigenetic factors raises concerns around curative rhetoric, particularly given the continued use of coercive measures around the world that attempt to change transgender individuals’ self-conceptions (i.e., “conversion therapy”) (46). Researchers who choose to investigate the potential epigenetic background of gender dysphoria will need to be exceedingly cautious in knowledge translation of their findings to minimize the instrumentalization of their research and to mitigate its use in further pathologization.

Second, such research may lead healthcare professionals to withhold the use of cross-sex hormones if these are found to be associated with specific epigenetic changes. While information on the potential health impacts of hormonal treatments is crucial for the provision of informed consent, as well as for determining the safest and most effective ways to deliver hormones when appropriate, it will be important for physicians to keep in mind that a certain degree of physical risk may be ethically outweighed by expected psychosocial benefits depending on the needs and values of the given patient. Further, access to medical transition when appropriate is itself considered a life-saving treatment, demonstrating a significant increase to quality of life and decrease in suicidality in longitudinal studies, with a corresponding increase in suicidality in the face of undue barriers to transition (37).

Also, special attention will need to be paid to research with transgender minors. There remains a significant knowledge gap with regard to the potential short and long-term epigenetic effects of pubertal suppression and hormone replacement use in adolescence, and further long-term studies are needed. However, apart from the usual challenges of pediatric research, including questions around informed consent, transgender adolescents face disproportionately high risks of abuse within their homes compared to their cisgender counterparts, leaving them at higher risk of being coerced by others in their medical decision-making (43). Some scholars have suggested an ethical framework that exempts transgender and other LGBTQIA2+ (lesbian, gay, bisexual, transgender, queer, intersex, asexual, and two-spirit) youths with sufficient capacity from parental consent requirements in research, when seeking such consent would put the youth at risk, in order to make sure that this doubly vulnerable population is not excluded from research altogether (47).

Finally, it is important to remember that the transgender population is small, geographically dispersed and heterogenous in terms of exposures, self-understanding and experiences. This can lead to bias and a risk of over-generalisation of small studies. For example, methylation patterns are known to differ according to ancestry (48). Underrepresentation of the transgender populations from some countries, particularly the exclusion of those where gender variance is criminalised or heavily stigmatized, could lead to skewed results in epigenetic studies. Studies should be large enough and include extensive phenotyping to attempt to control for these factors and, at a minimum, consider separately trans women, trans men and non-binary populations.

## DISCUSSION

In this paper, we have presented three case studies of vulnerable populations of interest to epigenetics researchers and considered the various ways in which their vulnerabilities may be directly or indirectly increased via epigenetic research. In the case of Indigenous populations, for example, where there is already a long history of researchers contributing to harm via unethical and unconsented research, studies that seek to explain health disparities and epigenetic differences that have largely resulted from colonial interference may further entrench racialization and “othering” of already vulnerable populations (22). In the case of autistic populations, a focus on framing epigenetic differences as the results of environmental “deficits” may create further stigmatization and generate fear around behaviours and practices that may contribute to the autistic neurotype. Finally, research with transgender populations that seeks to examine the epigenetic differences that may lead to or result from social or medical transition could result in further unjust forms of gatekeeping that limit access to medical care for a population whose needs are already underserved. The thread tying these populations together in the realm of epigenetics research is that by engaging in this research, there is a risk of pathologizing traits of the vulnerable population in a way that increases their vulnerability, either by increasing the risk of stigmatization and discrimination, decreasing access to necessary care, or both. This is particularly the case when a social or cultural behaviour or experience is tied to a biological marker or outcome. There are additional challenges to conducting research with these populations, as widespread discrimination makes it difficult to disentangle “causal” variants from the population stress and lack of access to care and social and economic goods. Finally, in

all three cases examined here, diversity of these populations provides a further challenge, and researchers must be careful not to over-extrapolate.

## Points to Consider in Conducting Epigenetic Research with Vulnerable Populations

Despite these challenges, there are several ways in which researchers can mitigate the vulnerabilities that could potentially be caused by epigenetic studies:

### ***1. Involvement of the vulnerable population in study development, design, and progression from research question to knowledge translation***

Researchers should engage with community stakeholders from vulnerable populations from the earliest stages of research planning and identify ways in which their research can address the needs expressed by the population and otherwise be beneficial to them. This approach can be used by both researchers and funding bodies to set research priorities and to allocate funding accordingly. While this is important for all vulnerable-population research, it is particularly important in the epigenetic context, where the research may uncover epigenetic causal links between social behaviours and biological health outcomes that are intrinsically linked to questions of personal and community identity.

### ***2. Attention to the broader implications of the research beyond the immediate research question***

Researchers should attempt to foresee not only how their research will advance scientific understanding, but how it might affect the population more broadly. In the case of epigenetic research, this will mean paying particular attention to the ways in which research that examines behavioural and lifestyle factors might further stigmatize a culture or community, as well as the ways in which research examining the epigenetics of a vulnerable population might be used for an unasked-for curative approach.

### ***3. Free, informed, and supported consent***

Researchers should pay special attention to the particular challenges to consent raised both by the complexities of epigenetic science and research with vulnerable populations. Community members and advocates should be involved in the development of consent documents and procedures, with special consideration given to any additional needs of the population. Privacy risks should be assessed and communicated to participants based on an understanding that vulnerable populations may be at a higher risk in the case of a confidentiality breach, given the combination of medical with social and lifestyle information in epigenetic research, and considering its potential implications for others through shared environments. Researchers should also be cognizant of the potential for epigenetic research to provide information on intergenerational experiences. While privacy and confidentiality are of utmost importance in all research, vulnerable participants may face an increased risk of discrimination and violence if their privacy is breached, particularly to potentially abusive family members or discriminatory employers and researchers (49). Particular attention needs to be paid to the language that is used in developing consent forms and study documentation, using language that is respectful of an individuals' self-identification and ways of discussing their body and experience (for example, by encouraging participants to use whatever terminology is most comfortable for them in describing themselves) (6).

### ***4. Caution in the extrapolation from animal models***

While animal models provide an excellent opportunity to study inherited epigenetic effects, researchers should be careful in extrapolating from animal models to human research, particularly when the epigenetic factor being studied involves social or behavioral factors. Researchers should pay particular attention to the way that human presumptions around social, cultural, and gendered behavior become implicitly embedded in assumptions surrounding animal research.

### ***5. Study design***

Epigenetic researchers working with vulnerable populations should be aware of the potential harms of both under-inclusion and over-extrapolation. Because epigenetic research incorporates social and environmental context, extrapolation to individuals with similar vulnerabilities but who differ significantly in terms of geography, socio-economic factors, and other confounding variables risks returning skewed data. Researchers should attempt to include representative numbers of vulnerable populations in all epigenetic studies, not only those that target that population, and research that focuses on a vulnerable population should be careful to use appropriately powered studies to answer the questions being asked.

### ***6. Careful communication of results***

Epigenetic researchers should bear in mind the broader implications of their results for the populations concerned, even when they are not directly involved in further knowledge translation of their research. Researchers seeking to determine the underlying epigenetic mechanisms of adverse health outcomes in vulnerable populations should be conscious of the potential for this information to affect stereotyping and stigmatization, and to communicate their results in a culturally conscious way that recognizes this concern. When an additional vulnerability is identified in an already vulnerable population (e.g., epigenetic effect from an exposure), study authors should seek to mitigate this if it is in the expressed interests of the population (e.g., informing participants of individualized findings). As with all communication of scientific results, accurately depicting the strength of research findings and stressing study limitations will help guard against misinterpretation (50).

## CONCLUSION

When epigenetics and vulnerable identities intersect, there is a risk of increased pathologization of those identities and associated behaviours. In communities where medical research historically contributed to harms against that population, epigenetics researchers need to take into account not just what scientific advances might occur because of their research, but how the communication of their research results may feed back into positive or harmful stereotypes and narratives about that population. While this is true of research in general, epigenetics research, in examining the molecular effects of environments and behaviours, may risk furthering stigma in more profound ways than genetics-era research. The populations discussed here are of interest to epigenetics researchers for different reasons, including inheritance and cultural factors, neurodevelopmental epigenetics, and social epigenetics, and have been subject already to different levels of scrutiny by epigenetics researchers. However, they share the challenge of being groups that are of interest to researchers because of their marginalization and vulnerability, but who also risk being further marginalized in the pursuit of more answers. Ethical epigenetic research will need to remain conscious of the challenges of conducting research on vulnerability without increasing stigma and pathologization, and take the steps necessary to mitigate related harms.

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K. Saulnier était affilié au Centre de génomique et politiques lors de la rédaction de cet article et est maintenant affilié au Conseil de recherches en sciences humaines. C. Dupras est un ancien membre du conseil d'administration de l'*Revue canadienne de bioéthique*. Le contenu de cet article reflète leurs propres opinions et celles de l'équipe de recherche uniquement.

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### Conflicts of Interest

K. Saulnier was affiliated with the Centre of Genomics and Policy during the drafting of this article and is now affiliated with the Social Sciences and Humanities Research Council. C. Dupras is a former Executive Board member of Canadian Journal of Bioethics. The contents of this article are reflective of their own views and those of the research team only.

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