

Nature-versus-nurture considered harmful: Actionability as an alternative tool for understanding the exposome from an ethical perspective

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Abstract

Exposome research is put forward as a major tool for solving the nature-versus-nurture debate because the exposome is said to represent “the nature of nurture.” Against this influential idea, we argue that the adoption of the nature-versus-nurture debate into the exposome research program is a mistake that needs to be undone to allow for a proper bioethical assessment of exposome research. We first argue that this adoption is originally based on an equivocation between the traditional nature-versus-nurture debate and a debate about disease prediction/etiology. Second, due to this mistake, exposome research is pushed to adopt a limited conception of agential control that is harmful to one’s thinking about the good that exposome research can do for human health and wellbeing. To fully excise the nature-versus-nurture debate from exposome research, we argue that exposome researchers and bioethicists need to think about the exposome afresh from the perspective of actionability. We define the concept of actionability and related concepts and show how these can be used to analyze the ethical aspects of the exposome. In particular, we focus on refuting the popular “gun analogy” in exposome research, returning results to study participants and risk-taking in the context of a well-lived life.

KEYWORDS

actionability, agential control, ethics, exposome, genome, nature-versus-nurture

1 | INTRODUCTION

Prominent proponents of the study of the exposome argue that the Human Genome Project has caused a significant imbalance in our understanding of the nature-versus-nurture debate. Therefore, they argue that we must study “nurture”—the exposome—at the same resolution as “nature”—the genome. The exposome can be defined as the cumulative measure of environmental

influences and their associated biological responses throughout the lifespan.¹

¹Miller, G. W., & Jones, D. P. (2014). The nature of nurture: Refining the definition of the exposome. *Toxicological Sciences*, 137(1), 1–2. <https://doi.org/10.1093/toxsci/kft251>. For a historical account of the exposome and its account of “exposure,” see Canali, S. (2020). What’s new about the exposome? Exploring scientific change in contemporary epidemiology. *International Journal of Environmental Research and Public Health*, 17(8), 2879. <https://doi.org/10.3390/ijerph17082879>

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The tools and knowledge of our nature are far ahead of those for the environment. If we want to focus on the interaction between nature and nurture, we need better ways of cataloguing and integrating the complex exposures and forces that represent nurture. Such a framework is provided by the exposome.²

In short, exposome research aims to develop an integrated approach to cataloging and analyzing all (quantifiable) exposures that an individual encounters throughout their lifetime, including the bodily responses that those exposures cause. Researchers who advocate for the development of an exposome research program have argued that such an approach can bring a variety of needed innovations to the field of epidemiology.³

We agree that the exposome research program affords such much-needed innovations, but we will argue that the adoption of the nature-versus-nurture debate into the exposome research program is a mistake that needs to be undone to allow for a proper bioethical assessment of exposome research. Our argument revolves around two interrelated reasons. The first reason is that the adoption of the nature-versus-nurture was based on a mistaken conception of the goal of the traditional nature-versus-nurture debate.⁴ Consequently, the justification for relating exposome research to the nature-versus-nurture debate is not valid. Furthermore, we have found no reason in the literature for why we should think about exposome research from within the nature-versus-nurture framework that would satisfy the required burden of proof. The second reason is that, due to this mistake, exposome research is pushed to adopt an understanding of “nature” and “nurture” that is harmful to thinking about how exposome research can be used to improve health. To fully excise the nature-versus-nurture debate from exposome research, we argue that exposome researchers should reject the senses of “nature” and “nurture” as used by the traditional nature-versus-nurture debate and rethink how exposome research can be used to improve health. To execute this latter task, we concretize, define, and systematize the idea of actionability by drawing on existing exposome research.

²Ibid: 1.

³Vermeulen, R., Schymanski, E.L., Barabási, A.L., & Miller, G.W. (2020). The exposome and health: Where chemistry meets biology. *Science*, 367(6476), 392–396. <https://doi.org/10.1126/science.aay3164>; Miller, Jones (op. cit. n. 1): 1–2; Rappaport, S.M., & Smith, M.T. (2010). Environment and disease risks. *Science*, 330(6003), 460–461. <https://doi.org/10.1126/science.1192603>; Wild, C.P. (2005). Complementing the Genome with an “Exposome”: The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology. *Cancer Epidemiology Biomarkers and Prevention*, 14(8), 1847–1850. <https://doi.org/10.1158/1055-9965.EPI-05-0456>

⁴We characterize the nature-versus-nurture debate as “traditional” instead of “historical” or “contemporary” because the nature-versus-nurture debate is a specific and long-standing debate that continues at least from Galton up to today. Furthermore, we describe the debate as it has been synopsized by modern literature on the topic. Arguably, the topic at issue can be traced as far back as Plato’s discussion in the Meno on whether virtue can be taught. Srivastava, S., Gautam, K., Kumar, S., & Singh, P. (2020). Nature versus nurture. In J. Vonk & T. Shackelford (Eds.), *Encyclopedia of animal cognition and behavior* (pp. 1–9). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-47829-6_547-1; Badcock, C. R. (2015). Nature-nurture controversy, history of. In J. D. Wright (Ed.), *International encyclopedia of the social & behavioral sciences* (2nd ed., pp. 340–344). Oxford: Elsevier. <https://doi.org/10.1016/B978-0-08-097086-8.03136-6>

To help advance the exposome research program, we analyze a number of ethical aspects of exposome research with our conception of actionability. In particular, we discuss: how to best refute the popular “gun analogy” in exposome research, the topic of returning results to study participants, and risk-taking in the context of a well-lived life. As there is much more to be said on the topic, we welcome experts in other fields to comment on the practical utility of our understanding of actionability for their research.

2 | THE TRADITIONAL NATURE-VERSUS-NURTURE DEBATE WITHIN EXPOSOME RESEARCH

Since Galton, the nature-versus-nurture debate centers around the determinants of a person’s character.⁵ Is a person’s character determined by their “nature,” such as certain innate (genetic) properties? Or is a person’s character determined by the nurturing that they received during (pregnancy and) childhood? Occupying a third position, so-called interactionists hold that some combination of both factors determines a person’s character. Last, a fourth position argues that the debate presents a false alternative because it is premised upon the false assumption that one’s character is determined by forces outside one’s control (whether “nature” or “nurture”).⁶ The resolution of this debate has many consequences throughout science because it has a major influence on one’s view of human nature. Are we by nature utility-maximizers, or is utility-maximization a way of acting that is not natural for the human species? Do human beings naturally develop social skills, or do we need schools to teach children social skills? The basic way in which one answers these questions results from one’s (implicit) view of the nature-versus-nurture debate. Any research that claims to provide an empirical answer to the nature-versus-nurture debate would thus have major effects that reverberate throughout the sciences.

Can exposome research help to provide an empirical answer to the nature-versus-nurture debate? Several exposome researchers answer in the affirmative, as they hold that the exposome is of one of the protagonists in the debate. So let us look at the way in which two influential papers argue for the connection between the exposome and “nurture,” and by extension, for the adoption of the nature-versus-nurture debate within exposome research. In 2010, five years after the exposome was coined, Rappaport and Smith wrote:

With successful characterization of both exposomes and genomes, environmental and genetic determinants of

⁵Srivastava, S., et al., op. cit. note 4, pp. 1–9; Badcock, op. cit. note 4, pp. 340–344.

⁶This assumption removes the option that we create our own character through our choices in life with the power to choose otherwise. For more on this view and the biological understanding of free will that it requires, see Binswanger, H. (1991). Volition as cognitive self-regulation. *Organizational Behavior and Human Decision Processes*, 50(2), 154–178. [https://doi.org/10.1016/0749-5978\(91\)90019-P](https://doi.org/10.1016/0749-5978(91)90019-P); Peikoff, L. (1991). *Objectivism: The Philosophy of Ayn Rand*. New York: Meridian. Note that our view of (direct) control and actionability, which is discussed later, can be viewed as being dependent upon the basic form of choice that is discussed by these authors.

chronic diseases can be united in high-resolution studies that examine gene-environment interactions. Such a union might even push the nature-versus-nurture debate toward resolution.⁷

Four years later, Miller and Jones published their highly influential and much-cited article “The Nature of Nurture: Refining the Definition of the Exposome.”⁸ In their article, they take Rappaport’s and Smith’s thought about resolving the nature-versus-nurture debate one step further by explicitly characterizing the exposome in terms of “nurture”:

Historical debates concerning human biology and behavior have frequently focused on contributions of nature, i.e., the inherited characteristics with which we are born, and nurture, i.e., life’s influences after birth. Indeed, the concept of nature vs nurture has guided our understanding of human biology for decades, if not centuries. [...] The exposome captures the essence of nurture; it is the summation and integration of external forces acting upon our genome throughout our lifespan.⁹

Furthermore, Miller and Jones provide a number of important qualifications to the role of exposome research in the nature-versus-nurture debate, in order to avoid the kind of overpromises made by

the Human Genome Project. Although they argue that exposome research is “an integrated science of nurture,”¹⁰ they write:

This epic undertaking of biomedical science and technology [the Human Genome Project] was completed with amazing speed and celebrated with great fanfare. But the limitation of genetics to predict disease rapidly became obvious; as noted by Dr Venter shortly after the completion of human genome sequence, ‘We simply do not have enough genes for this idea of biological determinism to be right.’¹¹ [...] The simple distinction between genes and environment is blurred by knowledge that environmental exposures cause permanent genetic changes via mutagenesis and also have long-term impact on gene expression through epigenetic mechanisms. [...] Randy Jirtle, a pioneer in epigenomics stated ‘The nature vs. nurture argument is rapidly proving to be irrelevant, because we’re finding that the 2 forces interact in highly specific ways that alter gene behavior.’¹² Although Dr Jirtle suggests the argument is becoming irrelevant, the reality is that biomedical research is overwhelmingly focused on the gene side of this debate. The tools and knowledge of our nature are far ahead of those for the environment. If we want to focus on the interaction between nature and nurture, we need better ways of cataloguing and integrating the complex exposures and forces that represent nurture. Such a framework is provided by the exposome.¹³

These quotes reveal a discrepancy between the traditional description of the nature-versus-nurture debate and the way in which exposome researchers describe the nature-versus-nurture debate. This difference lies in the different causal effects of “nature” and “nurture” that are being investigated. Whereas the traditional debate questions whether “nature” or “nurture” *determines a person’s character*, exposome researchers’ conception of the nature-versus-nurture debate revolves around the question whether “nature,” “nurture,” or their interaction *can predict disease*. Because these questions concern different explananda, we need to keep them distinct from each other. When arguing that exposome research can help resolve the nature-versus-nurture debate, exposome researchers have mistakenly equivocated between the goal of the traditional nature-versus-nurture debate (understanding the determinants of a

⁷Rappaport & Smith, op. cit. note 3, p. 461.

⁸For a number of articles where its influence is explicitly visible, see Aurich, D., Miles, O., & Schymanski, E. L. (2021). Historical exposomics and high resolution mass spectrometry. *Exposome*, 1(1), osab007. <https://doi.org/10.1093/exposome/osab007>; Chung, M. K., Rappaport, S. M., Wheelock, C. E., Nguyen, V. K., van der Meer, T. P., Miller, G. W., Vermeulen, R., & Patel, C. J. (2021). Utilizing a biology-driven approach to map the exposome in health and disease: An essential investment to drive the next generation of environmental discovery. *Environmental Health Perspectives*, 129(8), 085001. <https://doi.org/10.1289/EHP8327>; Huhn, S., Escher, B. I., Krauss, M., Scholz, S., Hackermüller, J., & Altenburger, R. (2021). Unravelling the chemical exposome in cohort studies: Routes explored and steps to become comprehensive. *Environmental Sciences Europe*, 33(1), 17. <https://doi.org/10.1186/s12302-020-00444-0>; Sillé, F. C. M., Karakitsios, S., Kleensang, A., Koehler, K., Maertens, A., Miller, G. W., Prasse, C., Quiros-Alcala, L., Ramachandran, G., Rappaport, S. M., Rule, A. M., Sargiannis, D., Smirnova, L., & Hartung, T. (2020). The exposome—A new approach for risk assessment. *ALTEX—Alternatives to Animal Experimentation*, 37(1), 3–23. <https://doi.org/10.14573/altex.2001051>; Olympio, K. P. K., Salles, F. J., Ferreira, A. P. S. da S., Pereira, E. C., de Oliveira, A. S., Leroux, I. N., & Vieira, F. B. A. (2019). The human exposome unraveling the impact of environment on health: Promise or reality? *Revista de Saúde Pública*, 53, 6. <https://doi.org/10.11606/S1518-8787.2019053000649>; Sargiannis, D. A. (2019). The HEALS project. In S. Dagnino & A. Macherone (Eds.), *Unraveling the exposome: A practical view* (pp. 405–422). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-89321-1_16; Tremblay, J., & Hamet, P. (2019). Environmental and genetic contributions to diabetes. *Metabolism—Clinical and Experimental*, 100, 153952. <https://doi.org/10.1016/j.metabol.2019.153952>; Sargiannis, D. A., & Karakitsios, S. P. (2018). Addressing complexity of health impact assessment in industrially contaminated sites via the exposome paradigm. *Epidemiologia & Prevenzione*, 42(5–6 Suppl 1), 37–48. <https://doi.org/10.19191/EP18.5-6.S1.P037.086>; Kiosoglou, P., Borda, A., Gray, K., Martin-Sanchez, F., Verspoor, K., & Lopez-Campos, G. (2017). Characterising the scope of exposome research: A generalisable approach. In A. V. Gundlapalli, M.-C. Jaulent, & D. Zhao (Eds.), *MEDINFO 2017: Precision healthcare through informatics* (pp. 457–461). Amsterdam: IOS Press. <https://doi.org/10.3233/978-1-61499-830-3-457>; Dennis, K. K., & Jones, D. P. (2016). The Exposome: A new frontier for education. *The American Biology Teacher*, 78(7), 542–548. <https://doi.org/10.1525/abt.2016.78.7.542>; Sugimura, H. (2016). Susceptibility to human cancer: From the perspective of a pathologist. *Pathology International*, 66(7), 359–368. <https://doi.org/10.1111/pin.12418>

⁹Miller & Jones, op. cit. note 1, pp. 1–2.

¹⁰Ibid: 2.

¹¹McKie, R. (2001). *Revealed: The secret of human behaviour*. Retrieved August 1, 2022, from <https://www.theguardian.com/science/2001/feb/11/genetics.humanbehaviour>

¹²Duke Health. (2006). *Duke Health*. <http://www.dukehealth.org/health+library/news/9583>. Although Miller and Jones refer to this article, it is not available online anymore. We have corresponded with Duke Health, but after they investigated further, they weren’t able to provide us with access to the original text.

¹³Miller & Jones, op. cit. note 1, p. 1.

person's character) and the goal of understanding disease etiology.¹⁴ Therefore, the adoption of the nature-versus-nurture debate in exposome research is a mistake based on an equivocation between the traditional view of the nature-versus-nurture debate and a debate on disease prediction/etiology. Defenders of this mistake could present new arguments for adopting the nature-versus-nurture debate into exposome research, but no such arguments in the current exposome literature exist and thus the required burden of proof remains unmet.

However, we cannot simply note this equivocation and finish our argument by concluding that exposome researchers should reject thinking about their research in terms of the nature-versus-nurture debate. As we will argue, the nature-versus-nurture is tightly-linked to a constrained view of what individuals can or cannot control that is harmful for thinking about how exposome research can improve health. By adopting the nature-versus-nurture debate as a framework for understanding the exposome, researchers are encouraged to import this harmful conception of control into exposome research. Thus, to fully excise the nature-versus-nurture debate from exposome research, we need to discuss these harmful effects and attempt to undo them by uprooting the underlying conception of control. However, in order to understand these harmful effects for thinking about improving health, we must first clarify how exposome research relates the value of improving health to its goal of understanding disease etiology. This is what we will discuss in the next section.

3 | EXPOSOME RESEARCH, DISEASE ETIOLOGY, AND THE VALUE OF HEALTH

Exposome research is performed *not only* to increase our understanding of disease etiology or how exposures affect the human body. The exposome is researched because doing so allows us to discover knowledge that individuals themselves, health professionals, or policymakers can subsequently use to improve health by means of active measures that prevent or intervene. Thus, exposome research is not merely a descriptive enterprise but also includes a further normative element: it seeks to improve our understanding of the effects of the environment on human biology *in order to* improve

human health in various ways.¹⁵ This normative element is included in the exposome research program at its conception by the researcher who originally coined the idea of the exposome.¹⁶ Thus, exposome research is not merely a form of basic research but also contains an applied dimension. To concretize this point, let us look at the crucial paragraph of Wild's original 2005 article where he first uses the term "exposome."

The imbalance in measurement precision of genes and environment has consequences, most fundamentally in compromising the ability to fully derive public health benefits from expenditure on the human genome and the aforementioned cohort studies. There is a desperate need to develop methods with the same precision for an individual's environmental exposure as we have for the individual's genome. I would like to suggest that there is need for an 'exposome' to match the 'genome.' This concept of an exposome may be useful in drawing attention to the need for methodologic developments in exposure assessment.¹⁷

In other words, the exposome concept itself was coined to satisfy a need for methodological developments that can be used to improve human health. Exposome research is not merely a form of basic research that seeks to deepen our understanding of disease etiology; exposome research itself needs to create methods that can be used to improve human health. Wild strengthens this normative element of exposome research in a later article, where he stresses the importance of understanding the biological responses caused by exposures.¹⁸ To summarize his view of why we need the exposome concept: the value of regarding all exposures (and their biological effects) under the single header of the concept "exposome" is to improve exposure assessment and the discovery of mechanisms by which the body responds to exposures—not as an end-goal, but to "open up avenues to prevention through modulation of specific identified biological pathways."¹⁹

The fact that exposome researchers include the norm of improving health in their research program does not imply that basic or fundamental research which is focused solely on assessing the effects of the genome and/or the environment on human biology,

¹⁴In fairness to Venter, let us note that his comment in the above quote was made in the context of the traditional nature-versus-nurture debate in general and genetic determinism in particular, not disease prediction. Gannett, L. (2019). The Human Genome Project. In E.N. Zalta (Ed.), *The Stanford Encyclopedia of Philosophy*. Metaphysics Research Lab, Stanford University. <https://plato.stanford.edu/archives/win2019/entries/human-genome/>; McKie, op. cit. note 11. Retrieved August 1, 2022, from <https://www.theguardian.com/science/2001/feb/11/genetics.humanbehaviour>. Similarly, when Collins made a case for a US prospective cohort for the identification of genetic and environmental factors that contribute to health and disease, he did not include any mention of the nature-versus-nurture issue (even though an article by Chakravarti and Little that Collins cites does explicitly relate "nature" and "nurture" to improving health). Collins, F. S. (2004). The case for a US prospective cohort study of genes and environment. *Nature*, 429(6990), 475–477. <https://doi.org/10.1038/nature02628>; Chakravarti, A., & Little, P. (2003). Nature, nurture and human disease. *Nature*, 421(6921), 412–414. <https://doi.org/10.1038/nature01401>. Thus, it is also important to note that exposome researchers are not the first in history to attempt the usage of the nature-versus-nurture framework for other explananda.

¹⁵We recognize that the very concept of health is itself norm-setting and teleological, but outside of an explicit commitment to the value of health one can still descriptively investigate a normative phenomenon to assess what it is, which is the sense of 'descriptive' we use here. Lennox, J. G. (1995). Health as an objective value. *The Journal of Medicine and Philosophy*, 20(5), 499–511. <https://doi.org/10.1093/jmp/20.5.499>; Binswanger, H. (1992). Life-based teleology and the foundations of ethics. *The Monist*, 75(1), 84–103. <https://doi.org/10.5840/monist19927514>

¹⁶Wild, op. cit. note 3, pp. 1847–1850.

¹⁷Ibid: 1848.

¹⁸Wild, C. P. (2012). The exposome: From concept to utility. *International Journal of Epidemiology*, 41(1), 24–32. <https://doi.org/10.1093/ije/dyr236>

¹⁹Ibid: 29. For a critical-constructive perspective on the need for the exposome concept, see Safarlou, C. W., Jongasma, K. R., Vermeulen, R. (Manuscript in preparation). Defending the exposome from the environment: Addressing criticisms and mission creep.

without any further normative goal, is not valuable.²⁰ Indeed, such research is valuable precisely because fundamental descriptive knowledge is a necessary condition for knowing how to act. For example, suppose we wish to decrease a person's risk of getting cardiovascular disease (which is a norm/goal). In that case, we first need to know cardiovascular disease risk factors (a descriptive fact).²¹ For exposome research, the descriptive etiological knowledge that an understanding of the exposome itself gives us is a middle term that provides a necessary condition for knowing how to improve human health.

This section concludes our discussion of how exposome research relates its goal of understanding disease etiology to its goal of improving health. To make it possible for individuals, health professionals, or policymakers to use exposome information for improving health, exposome research requires a view of human beings as being able to determine their own course of action with respect to health. As we will argue in the next section, the traditional nature-versus-nurture debate features a tightly-linked perspective on control that is harmful for thinking about how exposome information can be used in the pursuit of health.

4 | EXCISING THE “NATURE-VERSUS-NURTURE” PERSPECTIVE FROM EXPOSOME RESEARCH

Discussions of the normative implications of the traditional nature-versus-nurture debate tend to come packaged with the idea that the facts under the header “nature” are unchangeable facts that we cannot control and that the facts that fall under the header of “nurture” are (environmental or manufactured) factors that are (somehow) under our control.²² Via its conception of control, the traditional nature-versus-nurture debate interfaces with normative ethics. For example, people connect praise and blame to factors of “nurture” because they are under our control and do not apply ideas of praise and blame to factors of “nature” because they are not under our control and are an immutable part of who we are. With respect to the exposome, the fact that we have to eat to survive is an immutable part of our biology that we simply must accept. But when it comes to our diet, we can pick between many different options that are open to normative judgment. Within the traditional debate on nature-versus-nurture, a classic example concerns a person's temperament. Depending on the extent to which a person's temperament is an

immutable part of a person's character or something that can be changed, psychologists can help their clients to accept the parts of their temperament that are not under their control as part of their identity and help change the malleable (i.e., changeable; pliable) aspects of their temperament. Let us assume that a person's temperament is an unchangeable inherited trait that is not under their control. Then, we would not be able to praise or blame that person for the state of their temperament because we simply have to accept their temperament as an unshakable fact of their psychology. But if we assume that a person's temperament is fundamentally under their control, then we would be able to praise or blame them for the state of their temperament.

In other words, the traditional nature-versus-nurture debate's perspective on control is a part of the debate that is tightly-linked to its concepts of “nature” and “nurture.” Because exposome research program leaders advocate the usage of the traditional debate's senses of “nature” and “nurture” within exposome research, they are automatically asking researchers to import into exposome research the debate's tightly-linked perspective on what is under our control and what is not. This does not mean that exposome researchers have consistently adopted this conception of control, nor that all exposome researchers make the various mistakes that we will discuss in their writing (we will address this issue at several stages of our argumentation). However, to facilitate a comprehensive analysis of the problems that we see with this idea of control and anticipate such mistakes in the future, our arguments proceed from a literal understanding of “nature” as unchangeable and “nurture” as changeable.

In our view, there are three major problems with this perspective on “what is under our control and what is not” within the traditional nature-versus-nurture debate that are harmful to one's thinking about the actionability of the exposome. In short, we will argue that this perspective presents an unduly narrow, conceptually poor, and static way of thinking about control. Our analysis of these three problems will thus show why more work is needed to remove the nature-versus-nurture perspective from exposome research successfully. To fully excise the nature-versus-nurture debate from exposome research, we need to present an alternative view of how to think about the actionability of the exposome.

Before we discuss these three problems, let us clarify the value of the concept “actionability” and the related concepts of “actionable” and “act on” by providing definitions of these terms and a simple example in which these concepts are used for the context that we have in mind (see Table 1). Actionability is the state of being actionable. Information is actionable if it capable of being acted on by an agent. For an agent to act on information is for them to use it as a consideration in the pursuit of value(s). These concepts allow one to canvass the various ways in which (scientific) discovery of facts can be used to pursue value(s).

For example, let us say that someone discovers that a biomarker test shows that they have a blood lead level (BLL) of 10.0 micrograms per deciliter. If this person considers such information in pure isolation of their other knowledge and their values, they won't see

²⁰Also, note that fundamental research itself is not value-neutral, as it is aimed at better understanding the world, that is, the value of discovering truths about the world.

²¹Vrijheid, M. (2014). The exposome: A new paradigm to study the impact of environment on health. *Thorax*, 69(9), 876–878. <https://doi.org/10.1136/thoraxjnl-2013-204949>; Lennox, op. cit. note 15, p. 508.

²²This is a general observation about discussions of nature-versus-nurture, which possibly could be traced back to discussions of innate versus acquired traits, or rationalism versus empiricism. Griffiths, P., & Linquist, S. (2022). The distinction between innate and acquired characteristics. In E. N. Zalta (Ed.), *The Stanford encyclopedia of philosophy*. Metaphysics Research Lab, Stanford University. <https://plato.stanford.edu/archives/spr2022/entries/innate-acquired/>

TABLE 1 Key terms and definitions for understanding actionability.

Key terms	Definition
Value	That which an agent acts to gain and/or keep
For an agent to act on information	For an agent to use information as a consideration in the pursuit of value(s)
Actionable (as something of information and for an agent)	Capable of being acted on
Actionability (as something of information and for an agent)	The state of being actionable

any reason to *act on* this fact. But let us suppose that this person knows that lead is poisonous and values their health. In such a context, if this person thinks about the significance of their test result, they can draw the conclusion that they should seek out medical advice. By performing such a reasoning process, this person infers that they can use the information provided by the test result as a consideration for pursuing their health, and by going on such a pursuit they *act on* their test result.²³ Through such an evaluative process of relating facts to values, seemingly insignificant scientific information (such as biomarker test results) can become *actionable*, which creates the information's *actionability*.²⁴ Thinking in terms of actionability allows one to focus on the ways in which the (scientific) discovery of facts can be used for the (novel) pursuit of value(s) by agents.

Let us now return to the three problems that we alluded to earlier.

The first problem concerns the *unduly narrow* perspective on actionability within the traditional nature-versus-nurture framework: its tightly-linked view of control focuses only on what is directly under our control and what is not directly under our control. Although it is true that some things are directly under our control and some are not, we can still control the conditions surrounding the things that are not under our control. This allows for interventions on the causal consequences of things that are themselves not under our control. Within the context of exposome research, someone might not have direct control over certain genetic predispositions or problems with air quality that increase the risk of cardiovascular disease. From the perspective of the traditional nature-versus-nurture debate's tightly-linked view of control, this is where one's view of the action-implications of "nature" and "nurture" is halted, as there is, in this hypothetical case, no way to alter these aspects of "nature" and "nurture" directly. However, one has the option to take preventative or mitigatory measures that decrease the risk of

cardiovascular disease, such as taking up exercise, improving one's diet, or choosing to stop smoking. Such measures do not change the original genetic predispositions or air quality, but they do leverage our knowledge about them to change the causal consequences of factors that are not under our direct control, with the purpose of mitigating one's increased risk of cardiovascular disease. Because the ideas of "nature" and "nurture" within the traditional nature-versus-nurture debate are tightly-linked to what is not under our (direct) control and what is under our (direct) control, we can easily lose sight of the wider category of action in which our actions are aimed at preventing or mitigating health risks. The "nature-versus-nurture framework" can thereby easily narrow the scope of one's understanding of actionability, as if we have to remain passive with respect to the causal consequences of things that we cannot control.²⁵ Although we cannot control unchangeable facts, we can often change things in reality that factor into the effects of unchangeable facts and thereby create a better outcome, for example, for our health (see the yellow band in Figure 1).

The second problem occurs once one equates "nature" with our genome and "nurture" with our exposome (which is common in exposome research, but is novel in the history of the traditional debate).²⁶ As we have mentioned, the concepts of "nature" and "nurture" come packaged with the traditional debate's tightly-linked conception of control: the genome is equated with unchangeable "nature" and the exposome with changeable "nurture" (see the "Traditional nature-versus-nurture view of what is under our control" in Figure 1). These adjectives cause problems for thinking about actionability. On the one hand, we can change our genome by means of gene editing or modulate gene expression through epigenetic interventions. On the other hand, even though we can theoretically control a person's whole exposome when locking them in a vacuum, in many cases we are simply unable to have the fine-grained control

²³For illustrative purposes, this example involves fairly simple reasoning. However, to make information actionable, it can also require a more complex conceptual integration, creative process, or even a separate scientific discovery process. Wheelock, C. E., & Rappaport, S. M. (2020). The role of gene-environment interactions in lung disease: The urgent need for the exposome. *European Respiratory Journal*, 55(2), 1902064. <https://doi.org/10.1183/13993003.02064-2019>; Tarr, R. (2019). Economic theory and conceptions of value: Rand and Austrians versus the mainstream. In G. Salmieri & R. Mayhew (Eds.), *Foundations of a free society: Reflections on Ayn Rand's political philosophy* (pp. 327-383). University of Pittsburgh Press. <https://doi.org/10.2307/j.ctvdmwzp5.18>

²⁴Importantly, this evaluative process is essential to translational research.

²⁵We have noticed that articles on exposome research sometimes do not mention preventative or mitigatory options when we believe that they could or should have mentioned them. But because such articles are highly condensed, it is often not possible to ascribe such an error of omission to the nature-versus-nurture perspective. However, in conversations with exposome researchers where they make such errors, we found that the traditional nature-versus-nurture perspective can be the source of this type of error.

²⁶Srivastava, S., et al., op. cit. note 4, pp. 1-9; Gannett, op. cit. note 14; Badcock, op. cit. note 4, pp. 340-344. Note that "nature" is often intended to refer to all units of heredity, which is not necessarily fully covered by the genome (we have in mind the epigenome here, for instance). Similarly, as we have implicitly indicated in section 2, "nurture" is often equated with the environment as a whole instead of merely how one was raised or parented.

required to change the relevant aspects of our exposome.²⁷ By this, we mean that some types of exposures are not malleable given the current state of science and technology, nor in every situation. For example, there are many cases in which people have limited access to dietary options or are unable to control air quality. In this respect, the genome and exposome cut across the categories of what is under our control and what is not (see how the black circle and yellow band overlap the genome and exposome in Figure 1). Although exposome researchers are generally aware of this fact, the (inadvertent) equation between “exposome” and “changeable factors” can still obscure one’s view to the genome’s actionable aspects and the exposome’s nonactionable aspects. For example, Miller encourages such thinking about the exposome when he argues that the exposome offers a good way of having a person holistically understand the effects of their actions on their health:

Since the exposome encompasses all of the malleable components of our health, it can serve as an excellent rubric to understand health, and the behaviors and actions that improve health or contribute to disease.²⁸

Note that this way of thinking about health makes the changeable aspects of the genome disappear from one’s thinking about the causes of health and disease, as the exposome is understood to include the sum of all malleable aspects of our health. Furthermore, note that this comment is a case in which the application of the adjective “malleable,” if not appropriately qualified for the purpose of such a rubric, can cause a combination of the first and the second problem that we described. An aspect of one’s exposome can be malleable *in an ideal situation* and need not be malleable *in a nonideal case*. For example, decreasing air pollution in a city is something that can only be done effectively through group action.²⁹ However, it might not be possible to do something about pollution in a city for a particular individual with unwilling fellow residents. If that individual is also unable to relocate, then it would not be possible for them to fully remove the air pollution part from their exposome. This means that there would be a part of their exposome that is not unqualifiedly malleable in their particular situation. Because the traditional nature-versus-nurture debate features a tightly-linked conception of control that focuses on what is under our control and what is not under our control *simpliciter*, it does not necessarily have the conceptual resources to properly analyze such nonideal cases. However, this is not where our understanding of the actionability of pollution ends because that

particular individual can still choose to reduce the amount of pollutants that enter their lungs and/or mitigate the negative health effects of pollution. For example, this individual could choose to install an effective filter into their home AC unit or adopt an exercise regime that helps maintain healthy lungs.

The third problem concerns the exclusion of the effects of scientific and technological progress in the traditional nature-versus-nurture debate’s tightly-linked but static view of what is under our control and what is not. Within the traditional debate and its tightly-linked conception of control, what is at issue is which factor—unshakable “nature” or malleable “nurture”—has the upper hand (or how they interact). This way of dividing up the world does not adequately consider (1) the human ability to leverage knowledge and technology in the pursuit of value(s) and (2) the fact that there is progress in science and technology. The progress of science increases our knowledge of the world. In particular, exposome research aims to provide us with an understanding of how all the various exposures that originate from the world around us and within us affect our biological functioning. Such knowledge allows us to rethink our course of action and act on what we have learned. For example, think of cases in which we learn of new disease risk factors and are able to reduce their impact or eliminate them altogether. Or in cases where we have no technology to alter the underlying biochemical mechanisms, we can still try other preventative and/or mitigatory actions (or in a worst-case scenario, improve palliative care).³⁰ The progress of technology provides us with tools that allow us to perform new types of actions or adapt existing types of actions in different and/or better ways, which could involve changing things in the world in novel ways. For example, technologies such as smart sensors, chemoprevention (i.e., personalized medicine), and epigenetic editing will allow us to discover interventions and preventative or mitigatory actions that can improve one’s health and quality of life in ways that were considered impossible in the past. Therefore, we think that it is helpful to think of the sets of factors in the world that are under our control and/or actionable as having the potential to be expanded by the progress of science and technology.³¹ In Figure 1, we have incorporated this phenomenon via arrows that indicate that the yellow band and black circle can grow to overlap more of the genome and exposome.

Because these three problems distort the way one thinks about the actionability of the exposome, we believe that it is harmful to one’s thinking about the exposome to maintain that the exposome is “the nature of nurture.” To fully excise these problems from one’s thinking about the exposome, it is not enough to merely drop the “nature-versus-nurture” perspective. The nature-versus-nurture perspective comes packaged with a tightly-linked view of control that provides an unduly narrow, conceptually poor, and static way of

²⁷Technically, one could say that the exposome and genome are entirely under our control because we can lock a person in a vacuum or destroy all of their chromosomes. However, we have chosen not to include such broad cases of precision/resolution of control in Figure 1, as these would require us view the entire genome and exposome as “under our control,” which would ruin the illustrative value of our simplified representation.

²⁸Miller, G. W. (2020). *The exposome: A new paradigm for the environment and health* (2nd ed.). Amsterdam: Elsevier. <https://doi.org/10.1016/C2017-0-00630-4>

²⁹Kerckhoffs, J., Hoek, G., Gehring, U., & Vermeulen, R. (2021). Modelling nationwide spatial variation of ultrafine particles based on mobile monitoring. *Environment International*, 154, 106569. <https://doi.org/10.1016/j.envint.2021.106569>

³⁰This is not to say that all advances in science improve our knowledge in such a way that we always directly discover a novel valuable action-alternative.

³¹The extent to which the set of things that are under our direct control and the set of things that are more broadly actionable can keep expanding is an empirical question which we do not have the space to discuss here.

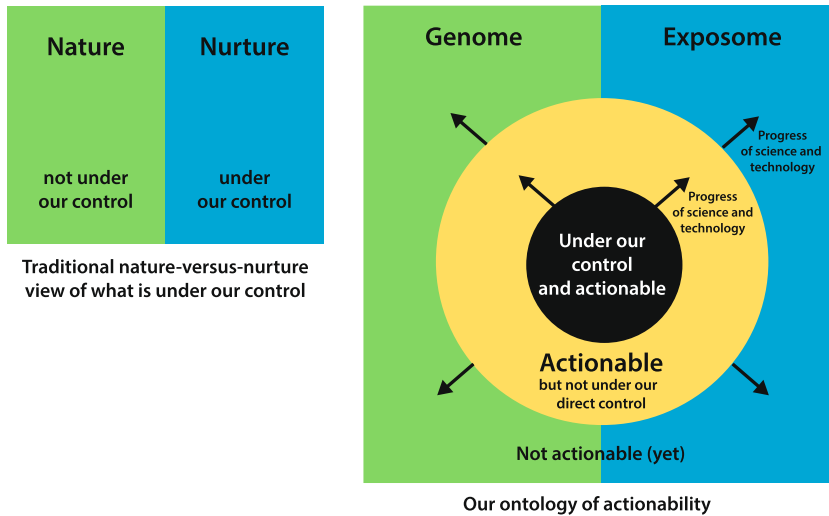


FIGURE 1 The traditional nature-versus-nurture's tightly-linked view of what is under our control next to our ontology of actionability. The (simplified) representation of our ontology is drawn from the perspective of the best of what is available in the world (not all individuals have access to the best of all science and technology).

thinking about what is under our control and what is not under our control. Thus, to fully excise the “nature-versus-nurture” perspective from one’s thinking, one needs to both reject the whole package *and* think about the exposome afresh through the lens of actionability.

That said, we believe that many exposome researchers are already advocating for much of what is included in our ontology of actionability. The most explicit instance of this phenomenon can be seen in a short paragraph by Wheelock and Rappaport on how to “actionise the exposome,” wherein they discuss how, ideally, the exposome would enable individuals to make specific lifestyle choices to alter their susceptibility to given exposures via the combination of personal wearables, clinical information, and genetic history.³² In this respect, our role is to systematize the purpose and value of the idea of actionability, make explicit ideas about control that remain implicit in articles on exposome research, and present a stark contrast between our understanding of actionability and the view of control that is tightly-linked to the traditional nature-versus-nurture debate.

In philosophical-ethical terms, the three problems we mentioned, together, go to the essence of the practical problem of adopting the traditional nature-versus-nurture debate in the context of exposome research. The conception of control that is tightly-linked to the traditional nature-versus-nurture debate radically dichotomizes the world into two factors: unshakable “nature” and malleable “nurture.” Much of the contemporary reaction against this type of thinking emphasizes the interaction between “nature” and “nurture” and argues that, in one way or another, we need to think in terms of mixtures between both factors (in which we might not even be able to distinguish either factor clearly).³³ But if our arguments about the

harmfulness of thinking in terms of nature-versus-nurture are correct, then we also need to reject the interactionist position as a good way of thinking about nature-versus-nurture, as this position is derived from the original dichotomy. Instead of letting the nature-versus-nurture perspective’s tightly-linked view of control drive our understanding of the actionability of the genome and exposome, we need to approach the question of actionability from an inductive perspective that takes into account the various ways in which human agents³⁴ can leverage their understanding of the genome and exposome (or the environment more generally) in service of human health and wellbeing.³⁵ Therefore, we do not hold that one should think about nature-versus-nurture in terms of mixtures but hold that one needs to reject the very senses of “nature” and “nurture” that are used in the traditional nature-versus-nurture debate and thus eliminate these usages of “nature” and “nurture” as concepts for thinking about the genome and exposome (or the environment, for that matter) from the perspective of disease etiology.

University Press. <https://doi.org/10.1215/9780822392811>; Traynor, B. J., & Singleton, A. B. (2010). Nature versus nurture: Death of a Dogma, and the road ahead. *Neuron*, 68(2), 196–200. <https://doi.org/10.1016/j.neuron.2010.10.002>; Pinker, S. (2004). Why nature & nurture won't go away. *Daedalus*, 133(4), 5–17. <https://doi.org/10.1162/0011526042365591>; Ridley, M. (2004). *Nature via nurture: genes, experience and what makes us human*. New York: HarperCollins; Khoury, M. J. (1998). Genetic and epidemiologic approaches to the search for gene-environment interaction: The case of osteoporosis. *American Journal of Epidemiology*, 147(1), 1–2. <https://doi.org/10.1093/oxfordjournals.aje.a009360>; Schulte, P. A., & Sweeney, M. H. (1995). Ethical considerations, confidentiality issues, rights of human subjects, and uses of monitoring data in research and regulation. *Environmental Health Perspectives*, 103(Suppl 3), 69–74. <https://doi.org/10.1289/ehp.95103s369>

³⁴Gorlin, E.I., & Schuur, R. (2019). Nurturing our better nature: A proposal for cognitive integrity as a foundation for autonomous living. *Behavior Genetics*, 49(2), 154–167. <https://doi.org/10.1007/s10519-018-9919-x>

³⁵In this respect, our ontology of actionability is not an exhaustive categorization of ways in which one can act on the genome or the exposome. For example, we have not included action-relevant dimensions such as uncertainty, risk, mediacy of control, time, weakness of will, the ideal/non-ideal situation distinction, the particular value that one is acting in pursuit of, the precision/resolution with which one can change parts of the genome and exposome, the distinction between the known and unknown parts of the genome and exposome, or which parts of the genome or exposome to prioritize for research such that they can be made actionable for particular values.

³²Wheelock & Rappaport, op. cit. note 22, p. 5.

³³Wright, R. O. (2022). Nature versus nurture—On the origins of a specious argument. *Exposome*, 2(1), osac005. <https://doi.org/10.1093/exposome/osac005>; Dupras, C., Saulnier, K. M., & Joly, Y. (2019). Epigenetics, ethics, law and society: A multidisciplinary review of descriptive, instrumental, dialectical and reflexive analyses. *Social Studies of Science*, 49(5), 785–810. <https://doi.org/10.1177/0306312719866007>; Miller & Jones, op. cit. note 1, pp. 1–2; Tabery, J. (2014). *Beyond versus: The struggle to understand the interaction of nature and nurture*. Cambridge: MIT Press. <https://doi.org/10.7551/mitpress/9780262027373.001>. 0001; Keller, E. F. (2010). *The mirage of a space between nature and nurture*. Durham: Duke

In this respect, our position resembles the aforementioned fourth position on the traditional nature-versus-nurture debate that rejects the validity of the traditional debate by arguing that the debate presents a false alternative because it is premised upon the false assumption that one's character is determined by forces outside of one's control (whether "nature" or "nurture"). As a corollary, this position also rejects the way in which the debate conceptualizes "nature" and "nurture" because both alternatives "deny nature in the only applicable sense."³⁶ However, as we discovered that the adoption of the nature-versus-nurture debate within exposome research is originally based on an equivocation, there has been no need, for our purpose of removing the nature-versus-nurture perspective from the exposome research program, to directly argue against the validity of the senses of "nature" and "nurture" as used in the context of the traditional nature-versus-nurture debate itself (even though our arguments can be used to that effect). What we have done in this section specifically is to argue that the senses of "nature" and "nurture" as used in the traditional debate are tightly-linked to a conception of control that is harmful for thinking about actionability in the context of exposome research.

As we alluded to in the title of this article, thinking in terms of actionability provides a tool for understanding the exposome from an ethical perspective. Up to this point in our argument, we have tried to show that this is true for thinking about the issue of control, in particular when contrasted with the traditional nature-versus-nurture debate's tightly-linked view of control. However, thinking in terms of actionability is also valuable beyond the issue of control. In the remainder of this article, we will illustrate how thinking in terms of actionability also affords ethical reflection on human agency and the interaction between axiology and normative ethics.

5 | ACTIONABILITY, AGENCY, AND AXIOLOGY

Within exposome research, the issue of agency arises most explicitly in Miller's analysis of the popular "gun analogy." In his monograph on the exposome, Miller argues against this analogy, which he has heard two directors of the US NIEHS use, as well as a director of the US NIH.³⁷

Genetics loads the gun, environment pulls the trigger.³⁸

Miller writes that he dislikes this phrase because of its very fatalistic tone, "as if the only thing the environment can do is pull the trigger" and because it suggests that "all environmental influences lead to catastrophic damage."³⁹ He argues that the latter is false

because our environment "can have beneficial effects on our health and can even contribute to the repair after damage" and that the environment can also render genetically endowed predispositions for disease "essentially moot."⁴⁰ He also argues that "careful regulation and manipulation of our environment can tie a knot in the barrel" and that "[o]ur destiny is not a loaded gun."⁴¹ As an answer to the "gun analogy," Miller proceeds to present what he labels as an absurd alternative version of the gun analogy and subsequently writes that

Alternatively, we could just stop using the original phrase and focus on the modification of our environment in a way that makes us healthier.⁴²

We agree with Miller in his assessment of the potential beneficial effects of the environment and his stress on the capacity of human beings to change our environment. However, we believe that the "gun analogy" can be more deeply uprooted by explicitly providing an alternative to the passive view of human agency that it operates on. This means that one needs to present a view of human beings as being fundamentally capable of mastering health. Individual human beings unravel the genome, build safe environments, develop personalized medicine, invent new vaccines; the list is almost infinite. This is the picture of human agency that we are arguing for in this article and that the idea of actionability affords. Genetics can load the gun and the environment can pull the trigger, but only creative human beings can disassemble the gun, apprehend the shooter, devise a bullet-proof vest, or arrange a preemptive strike. Instead of proposing that we stop using the analogy altogether or mentioning in passing that we can regulate and manipulate our environment, we should directly tackle the passive view of human agency that is at the root of the "gun analogy." To the extent that a person sincerely uses the "gun analogy"—to that extent this person is advocating a passive view of human agency that needs to be opposed. And to be able to fully counteract such a passive view of human agency, we hold that exposome researchers need to explicitly adopt our idea of actionability and promote its corresponding conception of human agency.

Furthermore, such an agency-based answer to the "gun analogy" prompts the question of what to do about the effects of the environment and our genetics. Are bullet-proof vests the best solution to gunfire? This is the point in our argument where normative ethics makes a difference for thinking about actionability. As we mentioned, we think of actionability as a useful term to canvass the various ways in which the (scientific) discovery of facts can be used in the pursuit of value(s). First of all, such a concept is valuable when doing "descriptive ethics" or descriptive axiology. But if we also think about actionability from the perspective of normative ethics, we gain a much broader view of exposome research and the ways in which it can improve our lives than when we think of actionability only in descriptive terms or in terms of "actionability for

³⁶Peikoff, *op. cit.* note 6, p. 204.

³⁷Miller, *op. cit.* note 24, pp. 43–44.

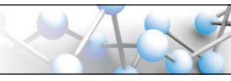
³⁸*Ibid.*: 43.

³⁹*Ibid.*

⁴⁰*Ibid.*: 43–44

⁴¹*Ibid.*

⁴²*Ibid.*: 44.



improving health.” To illustrate this idea, let us look at the case of someone who discovers novel occupational health risks through exposome analysis.⁴³ If this person is active-minded, this discovery will change the way in which this individual values their current job. For example, this person might strategically choose to stay in their job early in life and transition to a different kind of job once their health becomes more fragile later in life. Or, this individual could take the newly discovered risks for granted, knowing that these risks are an integral part of the work that they love. Another option would be that this individual attempts to create a safer work environment (an expression of this person's valuation of both their health as well as their work). Our point here is that the way in which one values one's health has consequences for many other values that feature in a well-lived life, such as work.⁴⁴ For reasons of space, we cannot fully analyze such cases without bringing in a substantive ethical theory. But if we want to be able to notice these kinds of (potential) consequences and thus have our eye out for them, then we need to understand that the actionability of the products of exposome research does *not merely* relate to our health.

Thinking about actionability from an ethical perspective is especially pertinent when it comes to returning results to study participants within exposome and genome research.⁴⁵ For example, in their influential article on the return of genomic results, Jarvik and colleagues use the concept of “actionable” only in the sense of “actionable with respect to health.” This can be seen most explicitly when they present studies that show that many research participants “would like more than highly actionable data, including data on nonactionable findings,” after which they name “information about minimally actionable conditions, ancestry information, and carrier status for recessive diseases.”⁴⁶ Their limited conception of actionability unduly narrows their thinking about the action- and corresponding value-implications of medical data to considerations of the individual's health, as it causes them to label ancestry information and carrier status for recessive diseases as “nonactionable findings.” One's perspective on the issue of actionability should be broad enough to encapsulate the fact that research participants can gain non-individual-health-related value from their

medical data,⁴⁷ such as information about their ancestors or potential to impact the health of their children.⁴⁸ This is not only true for genomic information that directly relates to values irrelevant to one's own health but also for health information that has consequences for one's other values. The clearest examples of such cases are those in which one discovers that one has a high chance of contracting a serious disease within a short period of time, such as metastatic cancer, Alzheimer's, or locked-in syndrome. If no prevention or intervention is possible, then one needs to re-evaluate the kind of life one can lead, as the viability of major life projects like having children or a long successful career could be severely impacted. Or take a more epistemically complicated case, such as when one discovers novel chemical products in one's blood for which no validated reference values exist. Depending on what we already know about similar chemical products, the value of the activity that increases one's exposure, and a rational approach to risk-taking, it could be good for one's wellbeing to, for example, either reduce exposure by stopping the activity or take the risk for granted and continue one's course of action. In order for us to be able to notice and actively think about these types of cases, we need to approach the actionability of biomedical research from an ethical perspective. In other words, when canvassing the various ways in which the (scientific) discovery of facts can be used in the pursuit of value(s), we need to think about how values can be consistently rooted in human life: we need to integrate the descriptive “is” of actionability with the moral “ought” of the standard of value.⁴⁹

6 | CONCLUSION

The adoption of the nature-versus-nurture debate within exposome research is based on an equivocation between the goal of the traditional nature-versus-nurture debate and the goal of understanding disease etiology. This equivocation explains why exposome research is pushed to adopt the traditional nature-versus-nurture debate's tightly-linked, unduly narrow, conceptually poor, and static view of control; a view of control that is harmful to anyone's thinking about how to improve health on the basis of exposome research.

⁴³Pronk, A., Loh, M., Kuijpers, E., Albin, M., Selander, J., Godderis, L., Ghosh, M., Vermeulen, R., Peters, S., Mehlum, I. S., Turner, M. C.g; Schlünssen, V., Goldberg, M., Kogevinas, M., Harding, Barbara N.g., Solovieva, S., Garani-Papadatos, T., van Tongeren, M., & The EPHOR Consortium, & Stierum, R. (2022). Applying the exposome concept to working life health: The EU EPHOR project. *Environmental Epidemiology*, 6(2), e185. <https://doi.org/10.1097/EE9.000000000000185>; Faisandier, L., Bonnetterre, V., De Gaudemaris, R., & Bicot, D. J. (2011). Occupational exposome: A network-based approach for characterizing Occupational Health Problems. *Journal of Biomedical Informatics*, 44(4), 545–552. <https://doi.org/10.1016/j.jbi.2011.02.010>

⁴⁴de Liège, T. F. (2021). *The role of production in human flourishing* (PhD Dissertation). University of California, Riverside. <https://escholarship.org/uc/item/87c5d065>

⁴⁵Coughlin, S. S., & Dawson, A. (2014). Ethical, legal and social issues in expositomics: A call for research investment. *Public Health Ethics*, 7(3), 207–210. <https://doi.org/10.1093/phe/phu031>

⁴⁶Jarvik, G. P., Amendola, L. M., Berg, J. S., Brothers, K., Clayton, E. W., Chung, W., eMERGE Act-ROR Committee and CERC Committee, CSER Act-ROR Working Group, & Burke, W. (2014). Return of genomic results to research participants: The floor, the ceiling, and the choices in between. *The American Journal of Human Genetics*, 94(6), 818–826. <https://doi.org/10.1016/j.ajhg.2014.04.009>

⁴⁷van der Schaar, J., Visser, L. N. C., Bouwman, F. H., Ket, J. C. F., Scheltens, P., Bredenoord, A. L., & van der Flier, W. M. (2022). Considerations regarding a diagnosis of Alzheimer's disease before dementia: A systematic review. *Alzheimer's Research and Therapy*, 14(1), 31. <https://doi.org/10.1186/s13195-022-00971-3>; Dyke, S. O. M., Saulnier, K. M., Dupras, C., Webster, A. P., Maschke, K., Rothstein, M., Siebert, R., Walter, J., Beck, S., Pastinen, T., & Joly, Y. (2019). Points-to-consider on the return of results in epigenetic research. *Genome Medicine*, 11(1), 31. <https://doi.org/10.1186/s13073-019-0646-6>; Bredenoord, A. L., Onland-Moret, N. C., & Van Delden, J. J. M. (2011). Feedback of individual genetic results to research participants: In favor of a qualified disclosure policy. *Human Mutation*, 32(8), 861–867. <https://doi.org/10.1002/humu.21518>

⁴⁸In the literature, values that are not related to the individual's health are often referred to as being of “personal utility.” However, because information about an individual's health has utility for that person, this is a confusing way to parse categories of value. Kohler, J. N., Turbitt, E., & Biesecker, B. B. (2017). Personal utility in genomic testing: A systematic literature review. *European Journal of Human Genetics*, 25(6), 662–668. <https://doi.org/10.1038/ejhg.2017.10>

⁴⁹Smith, T. (2000). *Viable values: A study of life as the root and reward of morality*. Lanham: Rowman & Littlefield; Peikoff, L. (1996). *Unity in epistemology and ethics [Lecture Recording]*. The Ayn Rand Institute eStore. <https://estore.aynrand.org>

To properly think about improving health with exposome research, we should think about the exposome from an inductive perspective that considers the way in which we can leverage exposome information in pursuit of human health and wellbeing and eliminate the usage of “nurture” as a concept for thinking about the exposome. As we have indicated, thinking in terms of actionability also affords further ethical reflection on human agency and the role of normative ethics for prescribing the valuable use of exposome research. Naturally, there is much more to be said on this topic, and we welcome experts in other fields to comment on the practical utility of our understanding of actionability for their research.

Exposome research's health-oriented aim should encourage researchers to stop using the “nature-versus-nurture” perspective for their thinking about the exposome research program. Instead of adopting Miller's and Jones's slogan that the exposome is “the nature of nurture,” we need to think of the exposome in terms of actionability: armed with an understanding of the effects of the environment on our body, how can we put this information to good use? As opposed to thinking in terms of nature-versus-nurture, such an actionability-based way of thinking centers around the potential of human agents to change the world by first understanding it. For example, the exposome research project EXPANSE, which the authors of this article are a part of, centers around the question: How to maximize one's health in a modern urban environment?⁵⁰ It adopts Bacon's dictum that “Nature, to be commanded, must be obeyed.”⁵¹ Correlatively—to use the exposome for improving health, we first need to analyze the exposome and adhere to its causal principles.

Our health and the factors that can improve or threaten it play a complex role in the interrelated set of values that make up one's life. In essence, exposome research aims to provide us with an important requirement for valuing one's health: causal biomedical knowledge that helps one to make better decisions about how to continually (1) improve health and (2) integrate the value of health with other values.

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