Beyond the central dogma: ecogenomics and the implication for bioethics.

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Abstract

In this chapter, we describe three areas within the broad field of ecogenomics or postgenomics: epigenetics, proteomics, and microbiomics. We argue that these fields challenge traditional bioethics in different ways. Since epigenetic, proteomic, and microbiomic data may contain phenotypical information, they may intensify discussions about consent, privacy, and return of results. But these fields also firmly position organisms, including human beings, as deeply entangled with their environments, as constituted by context, history, and experiences as much as genes. This yields new insights into concepts of health and development. We discuss precision medicine as an example of a systemic approach to health. We argue that acknowledging the entanglement of organism and environment also means recognizing the importance of interdisciplinarity for bioethics and thinking together biomedical ethics and environmental ethics.

Keywords

Proteomics, epigenetics, microbiome, environmental ethics, bioethics, precision medicine, personalized medicine

Introduction

Since the turn of the century, the once popular idea of the genome as 'the book of life' and DNA as the code that defines an organism's essence has lost much of its attractiveness. What genomic science and ever more sensitive techniques to analyze DNA have shown is, first and foremost, the complexity of cell biology and organisms in general. After the completion of the *Human Genome Project* in 2003, with the sequencing of almost the entire human genome, it became clear that there is more to life than what is in our genes. As such, the project's main results are said to be a recognition that there is much that we do not know. This realization has ushered in an area of systemic approaches to biology with the help of bioinformatics, sometimes referred to as *postgenomics* (1). Systems biology and *omics* are approaches that seek to tackle this complexity head-on and, with the help of advances in biotechnology, aim to unravel the complex interactions between genes and all the other components of the cell. What has become clear after decades of genetic research, also in medical genetics, is that more needs to be known about the interaction between gene expression and cell functioning and the environment. Ecogenomics is a term that is used, broadly speaking, to refer to the aim "to generate insight in the relationship between organisms (including microbes) and their environment, using various molecular techniques" (2). Within the *omics* field, several subfields deal with precisely this interaction. We will discuss three omics fields: epigenetics, proteomics, and microbiomics describing their relevance for bioethics.

Theoretical biologists and philosophers of biology have also reflected on life's dynamics and how the findings of the postgenomic age fit into that. For example, *Developmental Systems Theory* (DST) looks at organisms, and even evolution and inheritance, from the viewpoint of the entire matrix of resources needed to reproduce the life cycle. These resources, including epigenetic markers and proteins, and the cell as a whole, should be viewed as dynamic and entangled (3). A *process approach to biology* also stresses life's dynamics, changes, and interactions, thus reinstating a view on life that has never really disappeared since Heraclitus (4). Such approaches acknowledge that, besides genes, the environment is constitutive of organisms and their functions. Moreover, viewing genes and environment as different spheres that influence each other, with similar explanatory power, may be misguided. Nuclear DNA is part and parcel of the dynamics of the cell, and research into genes can yield important information about functioning and health. Nevertheless, it is a mistake to view genes as primary movers: the workings of DNA and 'genes' cannot be seen as separate from the cellular ecosystem or even the broader ecosystem.

Does this change anything for bioethical discussions? Few scientists or bioethicists today would still argue for a purely gene-centric view of life. At the same time, the view of the gene as a blueprint of life still haunts how we think about bioethical topics such as enhancement and the non-identity problem [81]. In what follows, we will suggest that taking the ontological commitments of systems biology and omics seriously can help shed new light on bioethical discussions. We will use three examples from *omics*: epigenetics, proteomics, and microbiomics. Applying these discussions to the case of precision medicine, we aim to show that if bioethicists take these new relational ontologies seriously, they can help researchers think through the implications of their research.

Epigenetics

Epigenetics, in its contemporary meaning, is an umbrella term for molecular mechanisms that govern gene expression. That there should be such mechanisms has been known for a long time: after all, each cell in our body contains, in principle, exceptions aside, the same DNA. Still, different cell types perform various functions, and individuals with identical DNA, such as monozygotic twins in humans, have different phenotypes. Well-known examples of such mechanisms are methylation

and histone modification, which control which parts of the DNA become accessible or inaccessible for transcription. Such epigenetic changes can be controlled by DNA, but they also happen under the influence of an external stimulus, the 'Environment'. 'Environment' is a very broad concept; It can refer to the milieu the cell inhabits within the organism and external influences such as the physical environment. The impact of particulate matter and pollution on methylation is well documented. But also psychological or social factors can influence gene expression. Think about psychological stress or the food we eat. Epigenetics is thus conceived of as 'biography becoming biology' (5,6). Hence, epigenetics is conceived as the molecular link between 'genes' and 'environment'. Although we generally acknowledge that both 'genes' and 'environment' are polysemous concepts, the concept of the 'environment' is vastly more complex. This should give bioethicists pause: perhaps discussions on the implications of such a molecular link, for example, for questions about responsibility, could start by considering what kind of environment is at stake and how the particularities of a specific environment influence the discussion.

The existence and necessity of a molecular link between DNA and environment is straightforward. At the same time, epigenetics has become widely known for the fact that epigenetic changes could be transgenerational, maybe even heritable. It may be so that what an organism experiences in its lifetime is transferred to the next generation. This seems to challenge assumptions about inheritance and brings back a Lamarckian aspect to biology (7). The jury is still out on whether human epigenetic changes can be genuinely inherited. Nevertheless, there is evidence that they can be transgenerational, as 'grandmothers' can influence the oocytes within the fetus they are carrying. Hence, there is an extended timeframe with regard to the influence of the Environment on an organism. This extended timeframe poses some extra challenges for bioethics and the question of *responsibility*. Bioethicists have thought for a long time about the responsibility of a pregnant person for their unborn child. Many would consider a pregnant woman engaging in binge drinking or smoking irresponsible if she knows the dangers to the future child's health. At the same time, epigenetic findings also show that what men do before they even consider siring children has an impact. It has been suggested that boys who smoke in their teens could unknowingly affect the health of future children(8). Do we hold fifteen-year-old boys responsible not only for their own health but also for future children they might (never) have [82]?

Another aspect that distinguishes the ethics of epigenetics from the ethics of genetics is that epigenetic markers, such as methyl marks, may be more easily *reversible* or even editable than genes (9). Although gene therapy and the editing of genes in somatic or even embryonic cells are still in their infancy, epigenetic editing may offer new and less invasive opportunities for treatment. Nevertheless, this in itself may raise ethical questions. For example, it has been argued that with the advent of *omics* studies and personalized and precision medicine, there is a shift to emphasizing preventive over curative approaches and enabling people to take responsibility for their health. Suppose editing or removing epigenetic markers resulting from specific lifestyles, such as smoking or environmental insults like pollution, becomes possible. Does this suggest a move back to curative medicine? Will this mean we can have an unhealthy lifestyle because we can always cure ourselves later? Of course, the fact that something can be fixed does not relieve us of the responsibility of preventing harm from happening in the first place. The same goes for systemic responsibilities such as pollution. It may be comforting to think that we can remove the epigenetic effects of pollution in the future. At the same time, the idea that we can cause harm first and fix it later will sit uncomfortably with many of us. There seems to be something inherently wrong with Environmental pollution, regardless of how curable the consequences are. But we may have to be more specific about this inherent wrong.

Many papers have been written about the *ethical, legal, and societal issues* (ELSI) of genetic research, specifically genetic privacy. In fact, genes have acquired a specific status in insurance and privacy law, rendering genetic privacy all-important. While it is true that genetic privacy is necessary, one may wonder whether this is not even more so with epigenetic privacy. Genome-Wide Methylation Analysis can yield epigenetic data (10). The more we know about the meaning and workings of epigenetics, the more these data will be interesting for third parties such as insurance companies or even the government. After all, genetic data is relatively fixed, and although interesting information can be gathered from them, it says little about a person's actual lifestyle and experiences. Epigenetic data, as biography becoming biology, may, in contrast, yield information about one's phenotype *and* experience. It may be that existing privacy laws may not be adequate to deal with this new knowledge.

Extended timeframe, reversibility, and genetic privacy are all topics that bioethics is well-equipped to deal with. It can rely on its standard toolbox of principles and empirical methods to evaluate these issues. As such, the bioethics of epigenetics need not be so different from the bioethics of genetics. However, there may be something more to learn from the mechanisms and meanings of epigenetics. Nowadays, when we hear about epigenetics, it is primarily the molecular mechanisms we mentioned before we think about. However, other related terms and meanings can shed light on what we can learn from the implications of epigenetics. They all refer to a more or less developmental view of life. Epigenesis, for example, is a theory on the development of organisms as formulated by the German physician and naturalist C. F. Wolff (11). It is best explained in contrast to *preformationism*, which assumes that an organism's eventual form is already available from conception. We could even consider the neo-Darwinist central dogma, with its insistence on the unidirectionality of DNA transcription and RNA translation, somewhat preformationist(12). *Epigenesis*, on the contrary, is the idea that an organism's form unfolds during development and that the form is also defined by the environment it encounters during development. Given that 21st-century epigenetics is said to provide the molecular link between genes and Environment, the connection with the much older term epigenesis is clear. Also, Conrad Waddington's *epigenetic landscape*, an idea from the mid-twentieth century, is related to our contemporary conception (13). The epigenetic landscape, with valleys and hills, describes a phenotype's development. Every cell has the same nuclear DNA, but they develop into specific types of cells depending on the place in the organism. Important here are the concepts of canalization (the adjustment of the developmental pathways to bring about a uniform developmental result despite genetic and environmental variations) and plasticity, the ability of a given genotype to give rise to different types of cells in response to environmental circumstances (13). The network or the landscape can change because there are changes in many genes. A minor rearrangement will not significantly affect the cells' trajectories because of the canalization. However, if the landscape is completely rearranged, this will severely impact development. It is important to note that canalization and plasticity are not opposites. They imply each other. Canalized development requires some plasticity to adapt to different circumstances. Furthermore, adapting to different circumstances means being fixed enough to withstand total annihilation. Indeed, stability requires dynamics to keep systems stable(14,15).

What molecular epigenetics, epigenesis, and Waddington's epigenetic landscape have in common is that they present a developmental perspective on life. An organism's form, specifically, and life in general, is not only the result of what is written in the genetic code. It is developing, maintaining its own and adapting to environments and experiences. There is a level of dynamism and unpredictability to life, of things we cannot control [83]. There is the importance of situatedness, of place. As bioethicists, we may have, understandably, bought into the idea that, in the end, we will know everything there is to know in our genes. In such a view, the most important ethical question

we should ask ourselves is what we can do and know in light of this heightened knowledge and control. However, what we can learn from epigenetics may be that there is also an aspect of unpredictability and lack of control. Reflecting on what this unpredictability means for ethics is equally important as reflecting on the question of what if we can create babies with specific desirable characteristics. Considering the entanglements of organisms and their physical and social milieu and the importance of place and chance encounters is ideally an interdisciplinary endeavor. We believe there is much leeway for bioethicists to engage with humanities and social sciences scholars such as anthropologists, human geographers, and sociologists to jointly reflect on the consequences of the blurred boundaries between biography and biology.

Proteomics

Another burgeoning *omics* field is *proteomics*. Proteomics studies proteins and protein structures that perform many different functions in organisms, such as the formation of structural fibers of muscle tissue, enzymatic metabolism and digestion, DNA synthesis and replication, and immune response and signal transduction. They can also be antibodies or hormones. Importantly, proteins are dynamic, three-dimensional complex systems: they undergo many changes over different time scales, reacting to changes within and without the organism (16). The proteome refers to either the entire set of proteins in an organism or a specific subset, such as, for example, the urinary or brain proteome. The main goal of proteomics as a field and approach in multi-omics analysis is a comprehensive, quantitative, and qualitative description of protein expression and its changes under the influence of biological perturbations, particularly those such as disease or drug treatment (17). Proteins and their dynamic folding are complex. Sebastian Mann and colleagues write in this respect that "The proteome is much more complex than the inventory of less than 20,000 protein-coding genes in the human genome would suggest, with potentially hundreds to thousands of variant proteins forming from one gene (known as *proteoforms*). Because of this complexity and various technical reasons, proteomics is less commonplace than workflows based on next-generation [genome] sequencing." (18). That might explain why substantial ethical engagement with proteomics has yet to occur. Although epigenetics is finding its feet in bioethics, and genetics has been bioethicists' topic of choice for decades, not many scholars have investigated the ethical issues surrounding proteomics; and those that have discussed it have focussed primarily on privacy, data sharing, return or results, and consent, topics that have been extensively discussed in genetics.

Indeed, one of the first questions that come to mind is how we should deal with the fact that protein analysis may also yield information about genes. For example, Sebastian Mann and colleagues have found that apolipoprotein E (APOE) allele status, associated with markedly increased odds of developing incurable Alzheimer's disease, can be inferred from the plasma proteome (18). Also, Philipp Geyer et al. have argued that serum samples may allow donor reidentification and sensitive information about health, sex, and race can be obtained from omics measurements other than genomics (19). Thus, in principle, proteomics data could yield not only information about one's genotype – a clear privacy risk - but also about more specific and sensitive information on one's phenotype and the current health status of a person. Precisely due to this potential for providing up-to-date insight in patients' health state, proteomics is positioned as an integral part of a precision medicine approach, and therefore, increasingly studied in the context of large cohort studies.

Both the fact that, at the moment, proteomics research is done in big datasets and the fact that it can yield more than genotype information raises interesting ethical and philosophical questions. First, there is a potential conflict between the enhanced demand for data privacy and the improved need for data sharing if such projects want to succeed. The question of who owns proteomic data

and who gets to access it is still unresolved (20). This discussion, of course, occurs against the background of more general controversies on balancing personal, commercial, and research interests in personal data. Indeed, as omics data such as epigenetics and proteomics contain information about a donor's history, future risk, *and* current phenotype, contemporary discussions based in genetics may not suffice. The integrated and systematic research of large-scale, multidimensional data can lead to the development of new biomarker panels and targeted treatment strategies. Their potential for the exploitation of clinical and economic value necessitates new data sharing and protection strategies (e.g., blockchain service providers). How can we endorse the 'good' that may come from large-scale systems biology approaches to health while at the same time safeguarding the participant's privacy? We may ask ourselves whether legislation such as GDPR (General Data Protection Regulation) or the European Health Data Space will be enough to ensure that the data shared with third parties cannot lead to problematic cases of reidentification or other forms of abuse.

The question of data sharing and privacy also ties in with the question about *consent*. Proteomics studies are typically large-scale and rely on state-of-the-art sequencing technologies and algorithmic models. For example, new technologies yielding new information may be developed after participants have consented. The type of consent that would yield the most flexibility for research purposes would be a one-time broad consent to any future research. However, we can ask ourselves whether this is fair to participants who may object to certain types of research that were not possible at the time of consent. Moreover, in the GDPR, it is stated that broad consent must be avoided. At the same time, repeated requests for approval in case of new uses of the data or chances to research protocols can lead to consent fatigue. The communication of results and incidental findings complicates the issue even further. As proteomics is an evolving science, the kind of information that can be extracted from proteins, be it geno- or phenotypical information, is also evolving. At the time of consent, it may be unknown which risk factors or actionable findings can come up, even in principle. Hence, it may be so that new studies and technologies can find relevant information not foreseen for existing cohorts. Or a finding once thought to be not actionable could become actionable when more is known about the interaction between proteins and specific drugs. It may be unfair to withhold relevant health information from participants if the information they got at the time of consent about the possible results the study might yield has become updated. At the same time, due to cohort size, sampling frequency, and data types and density, acquiring specific consent for follow-up or additional analysis can soon become very complicated. It may be necessary to come up with novel and dynamic consent types. Such consent types should balance respecting a participant's right to have a say on what happens with their samples and about what they will be informed of, without overburdening them or the researchers with extensive and repetitive consent procedures.

Return of results, incidental findings, privacy, and consent in the light of evolving science, are complicated because proteomics can also yield phenotypical information. At the same time, like epigenetics, proteomics may also change how we look at organisms. Proteins as dynamic structures that fold and change can teach us something about the *temporal* aspect of biology. Although genetic and also proteomic findings can teach us something about susceptibility to specific health issues, understanding the element of time may teach us something about resilience and change. If we look at banked samples of proteins, just as we have looked at banked samples of DNA, we risk forgetting that in the living human that donated the samples, the proteins have already 'gotten on with it'. Additionally, similar to genomics, proteomics is plagued by a (historical) dearth of dataset diversity and lack of standards for reporting sample populations. This may have significant downstream impacts on the performance of proteomics-based biomarkers and treatment on historically

marginalized patients. Moreover, this canonization of the so-called human proteome may limit the (robust) measurement and identification of so-called 'missing proteins'. Moreover, a protein's intricate folding and unfolding can not simply be deduced from the DNA but is performed in the cytoplasm. As proteomics is still in its infancy, the instruments used to study proteins cannot yet fully represent the dynamic 3D folding of proteins, nor (post-translational) modifications to these structures but necessarily have to simplify and idealize these complexities in order to study them. For example, in biomedicine, the technique most-commonly used to study proteomes is mass spectrometry, which analyses the mass of the protein and yields information about the protein's identity, chemical modifications, and structure (21). Philosophers of science such as Ian Hacking and Bruno Latour have written extensively about how the instruments used in scientific research not only enable and constrain what science can find but also the ontological assumptions behind these findings (22,23). Especially in the field of proteomics and systems biology, we also contend that bioethicists could benefit from understanding the impact of technological intervention on knowledge production. Hence, an engagement with the field of Science and Technology Studies (STS) could yield essential insights for bioethics, as this field has studied extensively how instruments define how we look at the world and what we deem important in what we study. A seminal book in this respect is *Rendering Life Molecular, Models, Modelers and Excitable Matter*, in which anthropologist Natasha Myers describes how protein modelers grapple with the complexity of the dynamic and living reality of proteins (24).

Just as researchers are eager to investigate this temporal aspect and the complex interactions of proteins and the cellular environment, bioethicists may think about how this complexity challenges the way we think about risk communication and consent. Just as current techniques cannot fully grasp the complexity of proteins, the tools and concepts bioethicists invented when we were still primarily thinking about genes (broad versus narrow consent, actionable versus non-actionable findings) may not suffice anymore. This may, even more, be the case when we consider that we are not only profoundly entangled with the material environment but also with myriads of other living beings on and inside us.

Microbiomics

Over the last decades, it has become clear that human organisms are not only deeply entangled with their material environment through epigenetics and proteomics. We are the host of trillions of microorganisms inhabiting our bodies (25). These microbial communities are influenced by several factors, including host genetics (26), mode of birth (27), diet (28), antibiotic exposures (29), environment, and lifestyle (30). The gut microbiome performs different functions. There is a symbiotic relationship with the host immune system (31). Moreover, the gut microbiome is also linked to the brain and behavior, mediated through immunological, neural, and endocrinal pathways (32). Hence, the term "microbiota-gut-brain (MGB) axis" (33). The fact that there are approximately as many microbial cells as human cells in the body (34) intimately linked with our mental and physical health raises interesting philosophical and practical ethical questions.

Indeed, the implications of microbiome research may further complicate specific bioethical questions. Like epigenetic and proteomic data, microbiomic data contains sensitive data that could identify the donor. They could also yield phenotypical information about lifestyle and health that may be interesting for insurance companies and other third parties. As stated previously, genetic and medical data is governed by strict regulations. However, stool samples containing relevant information about our gut microbiome are still considered waste, especially when they are not gathered in the context of medical research. It is suggested that current privacy regulatory

frameworks for genetic data and human tissue samples should be extended to include microbial samples (35). However, privacy issues are premised on conceptions of ownership, but, as Alice Hawkins and Kieran O' Doherty asked, "who owns your poop?" (36). What might once have been considered a silly question demonstrates increasing urgency and complexity in light of discussions concerning the symbiotic human-microbiota relationship, the increasing interest from the scientific community in microbiome research, and the increasing prevalence of so-called 'stool banks'. Bioethicists may reflect on what responsible stool management could look like and, notably, which forms informed consent might take.

Discussion on the return of individual findings is uniquely urgent in microbiome analysis as well. The return of individual research findings to research participants is becoming increasingly established as standard practice within genomics research and participatory research in biomedicine. Moreover, return of results policies are increasingly encoded in legislation through local interpretations of UNESCO's 'right (not) to know'. How should we handle such a right in relation to microbiomics? In genetic research, considerations of clinical validity and utility (actionability) are often leveraged as necessary conditions for the return of results. At face value, similar standards might apply to microbiome research. However, this new research context offers some unique challenges. Microbiome research has, up until now, relied primarily on (meta-)genome sequencing. These methods, however, have some significant drawbacks. For one, they might identify unexpressed genes within microorganisms or microbiota that are dead or non-growing (37). In this case, microbiome results from metagenomic sequencing do not conform to current standards of clinical utility. To mitigate some of these technological limitations, increasingly metagenomic-based microbiomics is replaced by so-called *culturomics*. In culturomics, samples are 'cultured' in different sample media before being sequenced to 'amplify' the sample and potentially bridge those (knowledge-)gaps. Culturing microbiota, however, 'displaces' one's microbiome by constructing an artificial environment surfacing questions on representability. Another significant drawback of culturomics is sampling bias due to a lack of knowledge on the conditions necessary to cultivate those 'missing links', again limiting its use for medical applications. Relatedly, culturing conditions primarily developed for Western samples might not easily translate to other cultures.

Besides research on stool samples, the possibility of transplanting microbiomes through fecal transplants has therapeutic potential to treat metabolic or even psychiatric conditions. At the same time, experiments in rodents have demonstrated that such transplants can yield personality changes. Questions on circumstances in which the benefits of the transplant outweigh the risk of personality changes are yet to be answered (38). Another significant area of medical microbiomics for ethical consideration pertains to nutrition. The connection between nutrition and microbiota has been well-established. For example, probiotic foods, including yogurt, have been marketed as beneficial for health for decades. More recently, it has been suggested that the impact of industrial meat production practices on gut microbiomes may be linked to obesity (38). Connections between (industrial) production practices and health outcomes through microbiome influence may necessitate increased regulatory standards to ensure food safety and scrutinize positive health claims related to probiotics (35). Simultaneously, however, it might also open the door to novel ways of biopolitical surveillance and 'healthism' concerning dietary choice. These discussions highlight gender dimensions in microbiomics, as women are disproportionally responsibilized for health-related decisions (39, 79).

Established links between health and microbiota also support a strong connection between health and environmental justice (39). Industrial exploitation, aggressive agricultural practices, and climate change destroy ever more ecosystems. Beyond the evident ecological impact, these practices might

significantly impact diverse (indigenous) ways of life. For example, local medical practices might depend on microbial lifeforms inhabiting such ecosystems. Moreover, enforced dietary change (e.g., due to a necessary shift in fiber cultivation) through environmental destruction might impact and disturb human-gut microbiome balances (40). Microbiomics might supply additional evidence for the disproportionate effects of climate change on indigenous communities. Interdisciplinary research between biomedical scientists, environmental scientists, (micro-)biologists, and bioethicists will be necessary to tackle and contain the many abovementioned issues.

As is evident from these questions within microbiome ethics, existing frameworks are not well-equipped to deal with the complexities offered by microbiomics. This might be related to fundamental yet neglected philosophical issues uprooted by these tiny creatures. Besides questions related to the application and management of knowledge in the microbiome field, the fact that we live in symbiosis with these organisms, and may even be partially defined by them, raises fundamental philosophical questions (84).

Thinking with microbes

When thinking about epigenetics and proteomics, we have conceived the environment as temporally, socially, and physically entangled with humans and health. Both fields potentially challenge dominant, Western ontological, and epistemological views of the subject as individualistic, atomistic, and self-sufficient. The microbiome further challenges these views. In this section, we explore this *thinking with* (40) microbes respectively in relation to (i) (philosophy of) science, (ii) concepts of disease, and (iii) the human as individual.

Traditionally, scientific objectivity has been conceived as aperspectivistic. To attain objective knowledge, scientists should aim to methodically subdue all subjective influences. All interindividual variability in perspectives must be negated to gain access to the so-called 'view from nowhere', which makes neutral knowledge possible. Accordingly, social and political values have no place in scientific practice. As a result, scientific knowledge is, to this day, often considered to be *value-free*. However, since its inception in positivist philosophy, this value-free conception of science and scientific knowledge has been challenged in various ways. Feminist scholars, in particular, have been critical of both the moral and epistemic legitimacy of the 'view from nowhere'-ideal to objectivity.

A particular episode in history kicked this thorough reconsideration of the attainability and desirability of this scientific and epistemological aperspectivism in a higher gear. The last decades of the 20th century were marked by scientific breakthroughs within fields such as biomedicine, biology, and anthropology (41). In many of these fields, 'thinking from women's lives' (42), bringing a gendered dimension to the table, brought into frame some questionable assumptions pervasive in the respective discipline. These advances were not achieved primarily by novel insights and tools within the scientific practice or by the influx of women in the sciences. They were prompted by (feminist and activist) interventions *from outside of scientific practice*. In medicine, for example, the Women's Health Movement challenged the idea of the male body as 'the gold standard' in clinical trials because it resulted in significant gaps in knowledge (41). Prompted by these developments, feminist philosophers of science started to consider how even our best science resulted in partial and incomplete knowledge. If current, aperspectivistic scientific ideals, standards, and methodologies lead to partial understanding, perhaps the ideal itself is flawed.

In response, feminist philosophers suggested that knowledge and knowledge-making practices are necessarily *socially situated* (43). The 'situated knowledge'-thesis states that non-epistemic values such as social position and identity influence what one *is in a position to know* (44). Who we are in a

hierarchically structured society and the material conditions in which we live shape our experiences, questions we ask, and answers we get. Taking this reasoning further leads us to ask, following Sandra Harding, 'Whose Science? Whose Knowledge?'(42). Indeed, science and knowledge can hardly be said to be aperspectival. What we know (and, importantly, what we do not know) is shaped by contingent historical, political, and social contexts. Feminist philosophers of science, accordingly, suggested that we should diversify the set of values and standpoints in scientific practice. Notably, the argument goes, this diversification of science is not merely morally justified but *epistemically* favorable. Thinking from and with the lives of Others may lead to better, more complete knowledge.

In the spirit of perspectival thinking and situated knowledge, and inspired by the cracks revealed in traditional organism/environment dichotomies by microbiome research, Formosinho and colleagues (45) propose the concept of *environmentality*. Environmentality entails "the state or quality of being a causal context for something else" (45). As an *epistemic* tool, environmentality expands what we consider environment and "help[s] us trace lines of relationality across scales, back in time, through flesh and across organismic boundaries" (45). The epistemic value of environmentality is operationalized by examining the role of the environment in a series of case studies. For example, the authors discuss a recent study in mice establishing a connection between maternal fiber intake, gut microbiota, and metabolic conditions in offspring. Applying environmentality to this case study reveals more complex relations between environment, mother, and offspring. Rather than merely considering the 'external' environmental effect of dietary intake, the *microbiota-fiber relation* constitutes the causal environment – the environmentality – for fetal metabolic development. Moreover, in this case, reconstituting the environment has the added effect of barring direct causal connections between dietary intake and offspring susceptibility to metabolic conditions, i.e., not all fiber intake is equal. Formosinho and colleagues propose that 'environmentality' is a fruitful tool for relational interpretations of data. As such, the concept seems equally suitable for epigenetic research (45). In this view, responsible science and a responsible way of looking at science transcend current dichotomies of host versus microbe or gene versus environment. Moreover, it calls for an appreciation of the perspectival body-in-context. We touch upon such implications for healthcare and biomedical research next.

Developments in microbiomics, epigenetics, and proteomics also challenge the idea of objective and purely scientific notions of health and disease. Philosopher of medicine Christopher Boorse famously argued for such a value-free concept of disease. His naturalistic account takes disease to consist of an internal state of (biological) dysfunction relative to a specific reference class (46). While naturalism has garnered critical scrutiny in the philosophical literature, its continued dominance in contemporary biomedicine and social imagination is undeniable. For example, we generally think of 'dysbiosis' in a very naturalistic way. Dysbiosis is viewed as the gut microbiome not functioning at 'normal' capacity and thus (potentially) incapacitating its human host. This conception also seems to inform our use of pharmaceutical/nutritional fixes to restore 'natural' balance in commensal microbial communities; think of probiotics to complement antibiotic treatment. But what is a normal microbiome? We can question that on many different grounds. First, there is significant interindividual variation in gut microbiome composition. So-called 'dysbiotic' people might be perfectly healthy, and 'unhealthy' individuals sometimes have 'statistically normal' gut microbiota (47). Furthermore, as there is no strict causality between dysbiosis and specific conditions, especially regarding mental conditions, one may question whether a simple one-way causal influence will ever be found. After all, what we feel and experience influences our eating and doing and vice versa. Just as Charles Dupras and Vardit Ravitsky have argued for epigenetics, the dynamic and reactive nature of the microbiome may challenge the notion of 'normal functioning' even more (48). In the context of the microbiome, a relational concept of health and pathology, such as the one championed by

French philosopher and medical doctor Georges Canguilhem may be more appropriate (49). There may not be such a thing as an intrinsically unhealthy microbiome, only one that is not adapted to its current environment. Moreover, we may ask ourselves *who* is healthy in the case of dysbiosis. Is it the human host of the microbes? Are the microbes themselves also unhealthy, or should we consider them part of the same superorganism?

Indeed, recent interest in microbiome research challenges metaphysical notions of subjectivity and individuality. As Stephen K. White notes, modernity has reconceptualized the human subject as disengaged from the world, entirely separated from and unaffected by its (cultural and natural) environment (50). This 'Teflon'-view of the self, as White calls it, completely separable from its lifeworld, functions to support grand narratives of mastery over nature and the construction of the neoliberal ethos of individualism. Visions of this modern self have also informed a particular framing of biology. Indeed, "Anatomical, physiological, and developmental criteria were conceived solely in terms of individuals, and the Darwinian view of life regarded aggregates of individuals of common ancestry as identifiable units in competition with one another" (51). The advent of systems biology, accompanied and facilitated by technological advances discussed above, challenges this view, raising interesting questions implicating issues far beyond the life sciences. We have already discussed epigenetics suggesting a relational ontology where the *external* world is implicated in the self. The microbiome, in particular, offers interesting perspectives on this *ontological* debate, and social and political questions - so intimately intertwined - could also benefit from considering an *internal* relationality. For example, if the microbiome lives through a symbiotic relationship with its human 'host' and vice versa, can we maintain the strict object-subject dichotomy exemplary of Western Enlightenment thinking? Our aim, however, is not to suggest replacing the object-subject dichotomy with an internal-external one. Rather, we aim to think *with* relationality "as ways to create the space for new ways of thinking about human individuality of all sorts" (52).

Such thinking about human individuality and relationality can be done on at least three levels: the purely biological, the metaphysical, and the social and political. With regard to the biological level, Rees and colleagues (53), for example, discuss microbiotic interaction with three biological 'bases for the self': the brain, the genome, and the (adaptive) immune system. The first two we have already discussed at length. Interestingly, the adaptive immune system typical of vertebrates, too, is heavily influenced by microbiome relations. For example, the microbiome plays a role in T- and B-cell expression. It also functions in immunoglobin response and activity. The microbiome, thus, aids in recognition of *nonself* and modulates immunogenic response accordingly (53). The intricate relations between the brain, genome, immune system, and microbiome offer the first argument that, at least in a *biological* sense, it is hard to maintain a notion of individuality without including microbiota.

Furthermore, the 'holobiont' thesis has gained some traction in philosophical debates on individuality. Holobionts are "symbiotic assemblages composed by a host plus its microbiome" (54). Accordingly, it transfigures the human-microbiome relation in a unified, symbiotic whole, i.e., a (biological) individual. Still, some scholars have argued that the idea of the holobiont does not do justice to the dynamics and fluidity of our relationship with microbes. For example, although the gut microbiome may be relatively stable, microbiomes on the skin come and go. Others have suggested an alternative to the holobiont idea and argue that the microbiome and host mutually constitute an (integrated) dynamic ecosystem. Suárez and Stencel (55) attempt to dissolve this dispute by suggesting that the human-microbiome relation might constitute both an individual (holobiont) and community (ecosystem) depending on the actor one takes to be central. No matter which side of the discussion one commits to, both interpretations agree on the co-constitutive nature of human and microbiota (45).

Beyond considerations of holobionts as *biological* individuals, human-microbiome relations equally bear on discussions within *social and political philosophy*. Philosopher Lisa Heldke, for example, contends that human-microbiota entanglements similarly apply to the social and political sphere (53). She gives the example of food. Before food finds its way into your refrigerator, it has been influenced by various social, political, ecological, and economic structures. All such 'external' factors effectively function to get politics into your fridge, through digestion it also finds its way into the body. Digestion demands the cooperation of both human and 'other-than-human' systems (saliva, gastric acid, gut microbiota, etcetera) to extract nutrients, ward-off unwelcome intruders, and excrete 'waste'. Thus, eating entangles us in a multidirectional matrix of relationships - symbiotic and parasitic, external and internal. Despite the ubiquity of the Teflon subject in contemporary western society, microbiome and epigenetics research shed light on a porous, plastic, fluid, dynamic, and situated more-than-human nature. Although these exciting debates are far from settled, they at least point towards a human individual that is 'holey' and 'with-y', constituted both by and with the in- and outside (53). Questions such as these demonstrate the fruitfulness of the interfacing of biology and philosophy. Moreover, this might call for a rethinking of the traditional division of labor between the humanities, arts, and the exact sciences, i.e., an imperative for broad interdisciplinarity (53).

At this point, the reader may think that the question of the human or microbial self is primarily of metaphysical interest. However, conceptions of individuality also permeate issues related to the ELSI of biomedical research. For many, it is straightforward that we have some ownership concerning the DNA and tissues that originate from our bodies. But what about a bioengineer studying a bacterial culture that originated in someone's gut? Should this also be considered *human* tissue, and is the engineer effectively working with donated human material, with all the ethical and legal consequences? Or should we consider this microbe as a separate being? Epigenetics, proteomics, and microbiomics challenge the fundamental concepts on which contemporary law and bioethics rely. Indeed, as the previous paragraphs suggest, current developments within the life sciences reorient some of the mainstays of Western thinking. Indeed, more complex notions of biology are steadily finding uptake within healthcare. So-called *systems medicine* aims to apply systems biology (and ecogenomics) lessons to biomedical research and clinical practice. Such an integrated view of health offers the potential to study the patient as a whole, entangled with the biological, social, cultural, and phenomenological (56). In the next section, we present recent developments in *precision medicine* as providing a window into a concrete attempt at translating biological complexity to clinical practice.

Precision Medicine: Biological complexity in practice

Functioning as a critical corrective to existing curative, fragmented, 'one-size-fits-all' healthcare systems, precision medicine[1] aims to radically reorient clinical care and biomedical science by implementing insights from systems biology in medicine (58). Drawing on technological advances such as ecogenomics, Big Data, and machine- and deep-learning algorithms, precision medicine strives to appreciate the complex, emergent nature of health as a necessary step to overhaul current *disease-centered* approaches in healthcare to a more *person-centered* vision of care. Instead of treating a patient 'one organ at a time', precision medicine recognizes the patient as a complex, unique, more-than-molecular whole. Although the precision medicine paradigm is still in its programmatic phase, its

[1] While the concept and applied terminology of personalized approaches to healthcare varies immensely depending on (cultural or medical) context and to the extent they engage with core tenets of systems biology or genomic medicine. Precision medicine, as we consider it here, offers the bold claim to provide an integrative, *holistic* view on the individual patient in their environment (57,58).

proponents envision some clear goals: (i) establish 'personal reference intervals' to appreciate the uniqueness and *individual variability of patients,* (ii) shift the focus of healthcare on prevention, through omics profiling and continuous monitoring, and (iii) combine heterogeneous (Environmental, molecular, lifestyle) data into a holistic and integrated view of health (56–60).

Biological complexity has been a central concern for precision medicine for both epistemic and moral reasons. Systems biology is leveraged to appreciate health's holistic nature and value patient variability to attain better care practices. Indeed "the strategies, technologies, and analytic tools of system medicine have given us the ability to *decipher biological complexity*, *making it possible* to provide care that is predictive, preventive, and personalized" (59). Consider the ontological underpinnings of precision medicine through dissecting operative conceptualizations of disease reveals its engagement with relational ontologies to be more limited than some proponents claim.

As philosopher Marianne Boenink argues, precision medicine is primarily committed to a *physiological, process view of disease* (61). This procedural approach to disease underpins some of the central claims of precision medicine in two distinct and coexisting ways. Nevertheless, each evinces a somewhat limited engagement with biological complexity. First, precision medicine relies on disease as "a stepwise, steadily growing cascade" (61). This 'cascade model of disease' suggests that each level along the molecular pathway from genotype to phenotype represents a step in disease progression and possible intervention targets (57,61). Precision medicine's commitment to prevention and early detection and, more specifically, the role envisioned for multi-omics analysis are evocative of such a molecular cascade. Different omics analyses are implemented at several 'levels' to provide (early) identification, 'real-time' assessment, and prognostication of an individual's health (risks) (59,62). For example, while early detection of the APOE e4 gene alerts one to a significant risk of *developing* Alzheimer's disease, proteomics is currently applied to identify biomarkers to assess and predict Alzheimer's disease progression (63). The (implicit) connection between profiling, prognostic, and preventive capabilities offered suggests that the spirit of the central dogma – perhaps through association rather than strict causation (64) - is very much alive in precision medicine.

At the same time, a less linear, more dynamic, and entangled process view of disease has also influenced precision medicine (61). By integrating environmental, lifestyle, epidemiological, and molecular data into complex, evolving, personalized data models (the pinnacle of which is referred to as a patient's 'digital twin'), precision medicine aims to (continuously) consider the individual patient in her specific and changing environment. These ambitions, often explicitly framed as breaking with current clinical practice, are meant to evoke congruence with relational conceptions of (human) biology. However, despite recognizing human-environment interactions, many of these attempts seem to subside in 'somatic reductionism' (56,61,65). Molecular endpoints (easily identifiable and quantifiable) are often considered prime candidates to identify the determinants of environmental and social diseases. For example, in projects studying the interaction between humans and the environment through epigenetic profiling, the environment, and its physiological effects are often reduced to related (internal) biological structures (66,67). Such reductionistic interpretations of human-environment interaction in health involve the risk of diverting attention from collective and structural remedies to mitigate environmental harm by reifying and reindividualizing health-environment interactions (68). Furthermore, it could lead to the dismissal of specific environmental or socio-cultural factors (e.g., racism or microaggressions) because those factors are less suitable for quantification (68).

Regardless of the view one takes to be exemplary of precision medicine as a whole (see footnote 1), omics technologies are currently positioned to identify and quantify *biomarkers*. Biomarkers are "characteristic(s) that (are) objectively measured and evaluated as an indicator of normal biological

processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (69). Metaphors evoked in relation to biomarkers are suggestive of the ontological assumptions that undergird precision medicine (70). omics are said to provide a 'molecular fingerprint '(61,71) , 'snapshot', or 'video'. While the former invokes stability reminiscent of a static genome, the idea of 'biomarkers' as videos echo more dynamic views on health related to systems biology. Despite these differences, perhaps reflective of the tensions within precision medicine's disease ontology identified earlier, these metaphors invoke the image of biomarkers and omics as providing a (quantifiable) "window in health and disease" (72). Echoing earlier remarks on the co-construction of reality through scientific and technological practices, omics technologies within precision medicine not only forward a quantified view of human biology. Visual metaphors in biomarker research, in particular, frame health as primarily located within the confines of the body.

The ontological commitments sketched above suggest that precision medicine reflects a particular notion of biological complexity: a *technoscientific holism* (73). Although complex processual views of life undoubtedly inspired the precision medicine project, these ambitions are tainted by a continual reliance on the body as a mechanistic, potentially quantifiable whole. Moreover, naturalistic conceptions of disease seem very much alive as health is defined as ultimately knowable, controllable, and manipulable through the methods and interventions of contemporary biomedical science. This approach might obscure illness' inherently normative, social, axiological, and existential nature (49, 74). We may also wonder where this leaves precision medicine concerning the role of the environment in health. In considering disease as wholly taking place within the confines of the individual (biological) body, the environment is ultimately reduced to its molecular traces. As such, despite inclinations towards complex, relational, and processual notions of health and recognizing the epistemological import of biological complexity, precision medicine stops short of ontological engagement with more-than-human, relational views on biology.

Furthermore, this ontological survey of precision medicine's implementation of process biology suggests a deep entanglement between ontology, epistemology, and ethics. This entanglement extends beyond discussions on data privacy, consent, and the return of individual results. Indeed, the idea of a mechanistic, molecularized, and quantifiable view of life informs a medical epistemology of health as knowable and a moral-epistemic imperative to inform oneself about one's health through molecular profiling and monitoring. Moreover, it may function to justify an individualist ethics of health. The latter is evident in precision medicine's 'envisioned patient'. Precision medicine's ambitions are premised on patients being 'active partners' and data-gatherers willing to share their data (57,75). While this participatory stance is said to empower patients, it might equally involve responsibilizing individual patients for their health (76,77). Importantly, the goals of patient activation and empowerment – f.e. through establishing personal health intervals – are built on a specific notion of health predetermined through the 'objective methods of science'.

Attending to precision medicine through the lens of relational ontologies, then, reveals a (problematic) aperspectivism embedded in the particular understanding of biological complexity driving its ethos. Taking relationality in health seriously does not simply entail recognizing our plasticity, environmentality, and historicity. It also demands recognition of the best of our medical knowledge and knowledge-making practices as similarly situated, partial, and ultimately up for debate. Moreover, person-centered care in light of situated knowledge and biological unpredictability foregrounds the need for epistemic humility in the co-constructive relation between carer and cared for (78). Minimally, this entails a reconsideration of dominant ahistoric, value-free, disembodied, and categorical conceptions of health. Genuinely *personalized* medicine might start from a relational concept of health emerging from the entanglement of the social, molecular, digital, and

environmental. As the speculative thread weaved throughout this chapter suggests, such more-than-human entanglements demand more-than-human ethics.

Conclusion: interdisciplinarity and environmentality

In this chapter, we have investigated how scientific fields such as epigenetics, proteomics, and microbiomics necessarily bring with them new ethical questions. We have described how ethical issues discussed at length in the context of genomics, such as consent, privacy, and return of results, are complicated by the fact that information that can be extracted from proteins, epigenetic markers, and the microbiome also contains information about the phenotype. Such phenotypical information may be even more attractive to third parties or relevant to the person from whom the sample originated. But these exciting developments within the postgenomic life sciences here gathered under the rubric or *ecogenomics* offer equally exciting prospects for philosophical and (meta)ethical reflection. These developments could also inspire bioethicists to deal with practical-ethical questions in novel ways. Postgenomics or ecogenomics brings to the fore at least two implications for bioethics: the need for interdisciplinarity and the need to bring environmental ethics and bioethics closer together.

First, epigenetics, proteomics, and microbiomics seem to firmly ascertain the plasticity, historicity, and environmentality of humans and other organisms. Moreover, these three fields seem to be intimately entangled. For example, the interplay between gut microbiome and epigenetics has been firmly established (80). Dietary changes seem to influence microbiome composition and affect the regulation of histone (de)methylation in the host genome (81). At the same time, the increasing evidence of the entanglement of an organism's biology with context, place, time, and experience calls for an expanding engagement of both exact science and bioethics with disciplines that have engaged with these factors. We have suggested that bioethics could benefit from an increased dialogue with fields traditionally outside philosophy, such as science and technology studies, anthropology, and human geography. They may offer necessary tools and exciting avenues to tackle the complex, interwoven, wicked questions we are currently facing. Bioethics could also engage with feminist philosophy of science and standpoint epistemology to reflect on the importance of including different and marginalized standpoints in science, but also in bioethics. Indeed, just as biology is entangled with context, science should also be seen as an activity taking place within a certain context.

Ecogenomics suggest how organisms, including humans, are partially defined by the material environment, for example, by the microbiomes that reside within us, on us, and around us. Nowadays, bioethics and environmental ethics are often seen as different disciplines. But the findings regarding the entanglement of health and environment should give us pause. Echoing the late Van Rensselaer Potter, ecogenomics urges the need for a *global bioethics*. Van Rensselaer Potter mourned the reduction of bioethics to medical ethics in the 1970s (81, 85). 'Doing good', of course, exceeds the confines of medical decision-making in many ways. At the same time, health is increasingly, on ever more complex levels, understood to transcend mere human biology. Ecogenomics teaches us that 'good' medical care cannot contend with neglecting the role of the environment. Environmental ethics, too, traditionally framed in discussion on anthropo- or ecocentrism, has much to learn from recent developments on biological complexity. Ecogenomics, thus, serves as a stark reminder that *we are the Environment, and the Environment is us*.

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