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Authors

Darling, Katherine Weatherford
Ackerman, Sara L
Hiatt, Robert H
et al.

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Enacting the molecular imperative: How gene-environment interaction research links bodies and environments in the Post-Genomic Age

Katherine Weatherford Darling[1], **Sara L. Ackerman, PhD, MPH**[2], **Robert H. Hiatt, MD, PhD**[3], **Sandra Soo-Jin Lee, PhD**[4], and **Janet K. Shim, PhD, MPP**[5]

Katherine Weatherford Darling: Katherine.Darling@ucsf.edu; Robert H. Hiatt: rhiatt@epi.ucsf.edu; Sandra Soo-Jin Lee: sandra.lee@stanford.edu; Janet K. Shim: Janet.Shim@ucsf.edu

[1]Sociology Doctoral Candidate, Department of Social and Behavioral Sciences, University of California, San Francisco, 3333 California Street, Suite 455, San Francisco, CA. 94143-0612

[2]Assistant Professor, Department of Social & Behavioral Sciences, University of California, San Francisco, 3333 California Street, Suite 455, San Francisco, CA 94143-0612

[3]Professor and Chair, Department of Epidemiology and Biostatistics, University of California, San Francisco, Box 0560, UCSF, San Francisco, CA 94143-0560

[4]Senior Research Scholar, Center for Biomedical Ethics, Stanford University Medical School, 1215 Welch Road, Mod A, Office 72, Stanford, CA 94305-5417

[5]Associate Professor of Sociology, Department of Social and Behavioral Sciences, University of California, San Francisco, Social Science and Medicine Submission, Cover Page, 3333 California Street, Suite 455, San Francisco, CA. 94143-0612

Abstract

Despite a proclaimed shift from ‘nature versus nurture’ to ‘genes and environment’ paradigms within biomedical and genomic science, capturing the environment and identifying gene-environment interactions (GEIs) has remained a challenge. What does ‘the environment’ mean in the post-genomic age? In this paper, we present qualitative data from a study of 33 principal investigators funded by the U.S. National Institutes of Health to conduct etiological research on three complex diseases (cancer, cardiovascular disease and diabetes). We examine their research practices and perspectives on the environment through the concept of molecularization: the social processes and transformations through which phenomena (diseases, identities, pollution, food, racial/ethnic classifications) are re-defined in terms of their molecular components and described in the language of molecular biology. We show how GEI researchers’ expansive conceptualizations of the environment ultimately yield to the imperative to molecularize and personalize the environment. They seek to ‘go into the body’ and re-work the boundaries between

Corresponding author: Katherine Weatherford Darling, Sociology Doctoral Candidate, Department of Social and Behavioral Sciences, University of California, San Francisco, 3333 California Street, Suite 455, San Francisco, CA. 94143-0612, Phone: 831-588-5473, Fax: (415) 476-6552, Katherine.Darling@ucsf.edu.

bodies and environments. In the process, they create epistemic hinges to facilitate a turn from efforts to understand social and environmental exposures outside the body, to quantifying their effects inside the body. GEI researchers respond to these emergent imperatives with a mixture of excitement, ambivalence and frustration. We reflect on how GEI researchers struggle to make meaning of molecules in their work, and how they grapple with molecularization as a methodological and rhetorical imperative as well as a process transforming biomedical research practices.

Keywords

USA; Gene-Environment Interactions; Molecularization; Environment; Genomics; Complex Disease; Health Inequalities

Introduction

In the decade after the Human Genome Project (HGP), genome scientists, medical geneticists, and science policy leaders worked to find new ways to identify and credibly establish the value of genomic science for medicine and public health. They did so by articulating the fields of genomic medicine, public health genomics, and precision medicine. These fields constituted new post-genomic combinations of techniques, methods, and disciplines that promised to yield more precise and robust explanations for disease and a future of personalized treatment and prevention. Gene-environment interaction (GEI) research emerged as one central formation of post-genomic science. GEI research examines genetically defined susceptibility to a range of exposures and the exposure-mediated regulation of gene expression (Frickel, 2004; Shostak, 2013). A shift from a “nature versus nurture” dichotomy to a focus on complexity and gene-environment interactions led to a growing “interactionist consensus” within post-genomic science (Landecker & Panofsky, 2013). This consensus required integrating knowledge about ‘the environment’ with genomics, and promised to empower researchers to leverage genomic science for public health. However, despite consensus about the existence of gene-environment interactions and their contribution to health and disease, researchers have found it challenging to define, measure, and analyze the environment in genomic science.

What does ‘the environment’ mean in the practice of genomic research? What do GEI researchers think about when they think about the environment? Drawing on data from longitudinal qualitative interviews and participant observation at scientific meetings, we answer these questions by showing how GEI researchers enact the environment in NIH-funded research on complex disease. This article offers a close-to-the-ground look at what GEI scientists involved in research on cancer, diabetes, and heart disease think about when they think about the environment. We examine how they incorporate and ‘enact’ the environment in their scientific practices, and how their efforts to do so are complicated by approaches that both exemplify, resist, and aspire to molecularization.

We first situate GEI researchers’ practices and experiences within the shifting landscape of post-genomic science in the U.S. Next, we discuss the concept of molecularization and introduce our concept of epistemic hinges. We then describe how GEI researchers in our

study operationalize and measure the environment in everyday practice. Their efforts reflect contemporary imperatives to personalize or individualize risk predictions, public health messages, and biomedical treatments. Thus GEI scientists' conceptualizations of the environment ultimately yield to the demand that they "go into the body" to most credibly capture the environment. We describe three different ways in which their practices re-work the boundaries and connections between human bodies and their environments. First, GEI researchers see bodies as environments in and of themselves and measure the impacts of various bodily attributes and lifestyles in terms of their effects on individuals' internal physiologies. Second, they see bodies as permeable — living in environments such that physical and chemical exposures of the external environment can be measured as chemical perturbations in the internal environment of the body. And third, bodies are seen as the materialization of social experiences, such that social phenomena like discrimination, inequality, and deprivation are manifested at the molecular level.

In each of these three modes, we demonstrate how GEI researchers create "epistemic hinges" between, on the one hand, social and environmental phenomena, and on the other hand, techniques for measuring the environment 'in the body,' measures of the body, and arguments about the body. The concept of an epistemic hinge highlights how GEI scientists conscript different disciplinary perspectives, methods and techniques, and even their own embodied experiences, to hinge 'social' and 'environmental' processes to 'biological' and molecular processes 'in the body.' These epistemic hinges thereby allow GEI scientists to pivot from their understandings of complex environments *outside* the body to their assessments of what occurs *inside* the body. Conceptually and methodologically, these epistemic hinges shift the focus 'into the body.'

However, some GEI scientists also questioned post-genomic promises of personalization. They find the molecular knowledge produced through GEI research to be quite distant from the practical applications and public health impacts that institutions like NIH and even they themselves hope to achieve. Yet, to garner credibility and manage complexity, our participants heeded the imperative to molecularize and replicate current ways of tracing the environment at the molecular level.

GEI scientists' encounters with the imperative to molecularize raise questions about what Shostak and Moinester have called the "political economy of perception" — the scientific and political questions of which "environments can be seen and which remain invisible" in post-genomic science (2015, p. 223). Paying attention to the politics of perceptibility — which risks we can see and how — can offer analysts and practitioners a lens for mapping how and why some technologies and methods for perceiving, operationalizing and measuring the environment may be "more or less social in nature" (Shostak & Moinester, 2015, p. 223). Some strategies for perceiving environmental exposures "include social institutions and processes, while others render 'the environment' an internal, individual attribute" (Shostak & Moinester, 2015, p. 223).

We argue that the dynamics we observed ultimately narrow the possibilities for understanding causal complexity rather than open up their potential. Epistemic hinges that rely exclusively on molecular methods and explanations ultimately narrow the causal

spectrum in ways that limit what we can know about complex diseases and the social inequalities at their root. In particular, these findings raise questions for scholars and public health practitioners interested in the "upstream" social conditions — the "causes of causes" — that shape health inequalities in the U.S (Krieger, 2011; Phelan, Link, & Tehranifar, 2010). While GEI researchers seek to integrate knowledge of 'biological' and 'social' causes of complex disease, the links they make also produce a specific trajectory of "causal accountability" (Krieger, 2008), in which responsibility for health risks resides within individuals. We also contribute to critiques of personalized or precision medicine (Tutton & Jamie, 2013) and other transformations that continue to individualize responsibility for managing health risks and preventing illness. First, recognizing the imperative to molecularize may create an opening for discussing the cultural authority of molecular knowledge and its privileged position over other ways of producing knowledge about complex disease. Second, understanding how scientists themselves are raising questions about the meaning and implications of molecular arguments, measures, and markers of risk may enable new ways of engaging with post-genomic scientists through critique as well as collaboration.

Post-Genomic Environments and Molecularization at Work

Scientific debates about gene-environment interactions date back to the early days of genetics (Tabery, 2014). More recently, GEI emerged as an orienting rubric for large-scale population studies and an area of institutional investment by federal research funders in the U.S. In the landscape of biomedical research funded by the U.S. National Institutes of Health (NIH), a few key milestones herald GEI research as emblematic of post-genomic science. Recent efforts led by the U.S. NIH explicitly sought to transform how biomedical researchers work with the environment and to alter the way U.S. citizens viewed their environment in relation to their health (Manolio, Bailey-Wilson, & Collins, 2006; National Human Genome Research Institute, 2014; Olden, Freudenberg, Dowd, & Shields, 2011). NIH leaders and senior investigators heralded a shift from "nature vs. nurture" to "genes and environment" (Khoury et al., 2011). Genome scientists increasingly acknowledged environmental complexity and turned their attention to a wider range of complicated causal processes that produce chronic diseases, including cancer, cardiovascular disease, and diabetes.

They did so by investing in genomic and molecular techniques and promoting ideas about personalizing biomedicine and public health. In particular, the National Institute of Environmental Health Sciences and the National Human Genome Research Institute launched the jointly organized Genes, Environment, and Health Initiative in 2006 (National Human Genome Research Institute, 2014). This collaboration sought explicitly to create a new vision of the environment that was more precise and more personalized, and less dependent on traditional methods now perceived to be indirect and insufficient, such as epidemiological questionnaires (Weis et al., 2005). After the Human Genome Project, then, the environment was increasingly viewed as a collection of individual attributes that should be measured at the molecular level. These shifts are re-shaping the political economy of perception, and in turn, efforts to link genes and environment.

The concept of molecularization provides a point of entry for understanding how GEI scientists create connections between bodies and environments, and the kinds of health risks we can see. Social scientists examining a range of scientific and biomedical fields have used the concept of molecularization to capture the re-definition of experiences and phenomena in molecular terms and the social or political ramifications of doing so. Molecularization is not only the re-definition of particular conditions, risks, and identities in molecular terms, but also a thorough transformation and reorganization of the institutions, methods, models, and vocabulary of biomedical science. These processes of re-definition and institutional change are closely linked to the possibilities for personal or individual choices about bodily transformations (Rose, 2006, 2007). Emergent molecular technologies, such as those that are currently transforming the nature of newborn screening (Timmermans & Buchbinder, 2010) and pre-natal genetic testing (Reed, 2009) have created new responsibilities, choices and ethical mandates within biomedical practice and everyday life.

In scientific domains with different histories of understanding 'the environment,' such as genetic toxicology (Frickel, 2004), toxicogenomics, or the environmental health sciences (Shostak, 2003, 2005), molecularization has re-defined and transformed the concepts and practices that animate and prescribe how to most credibly study the environment. For example, Shostak's (2013) account of the emergence of GEI research in toxicology and the environmental health sciences showed that the integration of genetic and molecular technologies with traditional methods in exposure assessment did not displace theories of environmental causation with genetic causes. Instead this promised integration transformed the environment into a phenomenon best measured and conceptualized *at a molecular level*.

A "molecular imagination" (Landecker, 2011) now imbues quotidian practices as well as common discursive strategies for describing social conditions and countering inequalities in health. In this sense, the shift away from the nature versus nurture dichotomy has expanded the jurisdiction of molecular biology and the potential applications of molecular measures and techniques to a wide range of phenomena previously understood through social or psychological metrics (e.g. social-economic status, stress, acculturation, economic deprivation, perceived racism). Molecularization thus shifts the science and politics of social connections as well as individual choices. Molecular technologies change how researchers understand social and environmental processes to 'get under the skin.'

Post-genomic scientists increasingly understand social and environmental forces as molecularly and biologically embedded across the lifespan (Lappé & Landecker, 2015). Landecker's (2011) recent work on nutritional epigenetics shows how food is recast as an environmental exposure, seen "as molecules that interact with our internal molecules," thereby producing "boundary dissolving" effects (Landecker, 2011, p. 185). Niewohner (2011) argued that with increasing appreciation of the molecular mechanisms of epigenetic regulation, researchers are less "able to ignore the many ties that link the individual body and its molecules to the spatio-temporal contexts" outside the body (2011, p. 290). In GEI research, then, molecularization aptly captures a dynamic shift in *what* researchers see as the environment and *how* the environment can be seen. Issues of how to intervene in disease risk — and who is responsible for modifying risks — are wrapped up with unsettled epistemic questions about how to best conceptualize, measure and change various environments.

We contribute to these discussions by showing that biomedical scientists such as the GEI researchers whom we interviewed and observed are active and reflexive participants in these transforming visions of 'the environment.' We argue that researchers experience molecularization as an ongoing, but not yet complete, transformation happening to themselves and biomedical science more broadly. They encounter molecularization — as well as personalization — as rhetorical and methodological imperatives that they work to enact, but yet also question. As we detail below, scientists' attempts to manage and understand causal complexity, from genetic to social and environmental risks, compel them to engage with the changing political economy of perception in GEI research.

Making Links Across the Causal Spectrum: Creating an Epistemic Hinge

To understand how GEI researchers negotiate this changing regime of perceptibility (Murphy, 2006) and manage causal complexity, we propose the concept of an "epistemic hinge." An epistemic hinge links incommensurable phenomena and translates between different ways of producing knowledge about bodies and environments. Our concept builds on social science research that details how molecularization is accomplished in practice, such as Nelson's "epistemic scaffolds" in behavioral genetics (2013) and Shostak's analysis of "technologies of translation" in genetic toxicology (2007). Here, we show how GEI researchers create epistemic hinges between complex, population-level, environmental and social phenomena on the one hand, and molecular mechanisms and explanations of human physiology on the other. GEI researchers study the effects of genetic risks, environments, and gene-environment interactions by going 'into the body' and enacting the molecular imperative wherever possible, creating hinges between bodies and environments.

In doing so, researchers conceptualize various aspects of the environment as ultimately and tangibly manifest in the internal processes and molecular milieux of bodies. The epistemic hinges GEI scientists create therefore facilitate a turn from understanding social and environmental exposures outside the body, to quantifying their effects inside the body. As an analytic metaphor, the epistemic hinge demonstrates how GEI researchers articulate chains of causation and accountability that seek to explain and attribute responsibility for health risks. In making these links, our scientist-participants simultaneously work to make ethical and political sense of questions about accountability for managing health risks and preventing illness.

Methods

This paper is based on a larger project, conducted in 2010–2014, in which we explored how principal investigators of gene-environment interaction studies mobilized and operationalized conceptions of race, ethnicity, and ancestry in their research. For that project, we recruited 33 NIH-funded principal investigators working with at least one non-white study population and conducting etiological research on one of three complex diseases: type 2 diabetes, cardiovascular disease, and cancer. Because the NIH mandates the inclusion of diverse populations (unless sufficient justification can be made for an exception) and the reporting of the racial/ethnic composition of study samples, we felt that focusing on NIH-funded investigators maximized the probability that our participants included measures

of race, ethnicity, and ancestry and considered their measurement and meanings in their research designs. In the process of being interviewed about their understandings and use of race, ethnicity, and ancestry measures in their research (Shim, Darling, et al., 2014; Shim, Ackerman, Darling, Hiatt, & Lee, 2014), the investigators very often invoked issues of the social environment and social determinants of health inequalities. That is, navigating questions of race and ancestry seemed to compel them to also consider questions of the environment. Thus, we undertook the present analysis of how these investigators see the environment, and attempt to enact those visions in their work.

The principal investigators in our sample reported a range of disciplinary affiliations, including epidemiology, genetic epidemiology, molecular epidemiology, genetics and interdisciplinary fields such as cancer research. Because many of the studies that they work on are well known, quite specific, and thus readily identifiable, we chose to remove or slightly alter some identifying information to protect participants' anonymity. For instance, study names and institutional affiliations are not provided. And in several cases, the disease outcome under study has been characterized in a more generic and generalized way (e.g., "cancer" instead of breast cancer, or "heart disease" instead of a specific cardiovascular condition).

We conducted 53 semi-structured longitudinal interviews, including 33 initial interviews and 20 follow-up interviews conducted twelve to eighteen months later. The anchor author and one research assistant conducted each initial interview. We posed open-ended questions about ongoing GEI research projects, researchers' professional trajectory and identity, their conceptions of the environment, scientific practices to incorporate and include environmental factors, and their reflections on the field of GEI research. We asked for concrete information on their past and current studies, what data they chose to collect and why, how they collected data on risk factors hypothesized to be related to disease outcomes, and what analytic procedures and choices were made. We organized a semi-structured interview guide by different phases of research (the design and recruitment phase, operationalizing and measuring the environment, and analyzing genetic and environmental data), and asked questions about their research practices, experiences, and perspectives in each phase in turn. We also customized our questions to participants' specific studies based on publicly available information about their current and past work. Follow-up interviews were conducted by the research assistant involved in the initial interview, and emphasized the progress of ongoing studies and elaboration of topics, activities and perspectives brought up in the initial interview. This paper also draws from two years of participant observation, totaling over 200 hours of observations and informal interviews, at nine scientific meetings held in North America. We obtained informed consent from research participants and our research methods were approved by the institutional review boards at Stanford University and the University of California, San Francisco.

Interviews were thematically coded using a codebook generated from inductive coding of 8 interviews based on the principles of constructionist grounded theory (Charmaz, 2006). We used the Atlas.ti Query Tool to generate thematic sets of quotations, including queries of descriptive codes for passages about operationalizing and measuring the environment, interpreting the significance of the environment or considering the environment in the

recruitment or design phase of research. We then wrote successive memos on codes and our interpretations concerning how the environment comes to be a meaningful concept in GEI research.

"You have to go into the body": Imperatives to molecularize and personalize

What do GEI researchers think about when they think about the environment? We heard repeatedly that the environment is "anything non-genetic." The environment, our scientist-participants explained, "is a wobbly word" that could include "anything, presumably, that isn't inherited genetically." Through this construction, conceptions of what constitutes 'the environment' are fundamentally structured by what it is not — the genome. 'The environment' expanded to include almost any risk factor, characteristic, or attribute beyond genomic sequence data that researchers could think of, including sex/gender, body mass index, smoking behaviors, physical activity, and exposure to toxins, nutrients, or pharmaceutical drugs.

However, we found that the conceptual elasticity of 'the environment' often gave way in the face of demands, from funders, reviewers, and colleagues, for more quantification and precise measurement. GEI researchers in our study articulated these demands as imperatives to molecularize and personalize the environment. As we detail below, GEI researchers enacted the imperative to molecularize through their routine collection of biological specimens, and experienced molecularization as a demand that they move their measures and methods 'into the body.' They argued that mustering "molecular credibility" (Kenney & Muller, forthcoming) — such as collecting and banking biological specimens for future analysis, measuring biomarkers or exposures in biospecimens, adding environmental measures to large genomic research consortia — has become requisite for good science in the post-genomic era. Yet even while GEI researchers sought to molecularize and personalize the environment, their practices did not always align with either these imperatives or their understandings of the health impacts of environmental and social complexity and social contexts.

We describe below three modes in which researchers experienced molecularization or personalization as imperatives and enacted the environment in their studies. First, researchers take bodies as environments in themselves; second, they see the body as a "molecular conduit" (Landecker & Panofsky, 2013) that links the environment external to the body to that which is internal to the body; and finally they understand the social environment as molecularly embodied. In each mode, GEI scientists sought to create an "epistemic hinge" from environmental exposures and social experiences to bodily (sometimes molecular) processes, measures and arguments. Throughout our discussion we pair scientists' modes of operationalizing and measuring the environment in ongoing research studies with the mixture of excitement, ambivalence, and frustration they expressed with regard to these practices. Their reflections on the potentials and limits of current methods and promises of personalized prevention and treatment revealed their own perspectives on the ethics and politics of responsibility for health.

Environments as Bodies and Individual Attributes

GEI researchers' practices and analyses sometimes conflated bodies, and measures of and in bodies, with the environment. That is, they included factors that researchers actively acknowledged were "not really an environment" but were bodily characteristics (e.g., sex, body mass index (BMI)) or health behaviors (e.g., physical activity, smoking, processed meat intake, history of hormone replacement therapy use) that were nonetheless understood to interact with or modify risk in the presence of genetic markers or loci. Similarly, they captured the environment by measuring substances (e.g., levels of omega 3 fatty acids, vitamin D and E, selenium) in biological specimens collected from the bodies of research participants.

One conference presenter put "environment" in scare quotes when talking about possible GEIs and their potential influence on breast cancer risk. In her research, she included factors such as parity, or how many children a woman has in her lifetime. She acknowledged that this was not really an "environmental" (using her fingers to indicate scare quotes) variable, but rather a known breast cancer risk factor that could modify the observed risk in populations defined by genetic markers. Her inclusion of parity as a research practice was not only based on known modifiers of genetic risk, but also the desire to include non-genetic behaviors and attributes that may not be 'environmental' per se, but by virtue of their non-genetic nature were categorized into the environment side of the equation. Similarly, another researcher studying cancer etiology described using individualized attributes of bodies such as obesity and hypertension as aspects of 'the environment,' under the rationale that these were "contexts in which genes operate." When we asked for clarification as to how he and his collaborators thought about measures of obesity and hypertension as constituting 'environmental' contexts, he elaborated:

> There's a biological model that we're following with obesity that has to deal with … circulating … hormones, and the role of obesity in hormone metabolism as well as the role of obesity in inflammation and other biological pathways [for cancer]. So, there's some direct hypotheses about the role of obesity in biological pathways and how that influences cancer risk in and of itself.

Thus this scientist saw variables such as blood pressure and BMI as bodily, and therefore measurable, proxies for modifiers to cancer causal pathways. In another example, a researcher explained that their transnational cancer study was "examining both environmental risk factors and surrogate measures of environmental risk factors." She included BMI and other measures of obesity, explaining that variables like "waist/hip ratio [act] as sort of a surrogate for, are you consuming more calories than you need? And therefore, you're somewhat obese versus lean."

Measuring the environment 'in the body' had become routine. A third cancer researcher, whose typical study design included the collection of meticulous, self-reported data on diet and physical activity with food and exercise diaries, described preparing a grant proposal to examine the association of these behaviors with cancer outcomes. As she reflected out loud to us, "you kind of would like to think that the strength of that study, with having such intense quality of life and good quality clinical data, might be enough" to score well in a

scientific review. But, she told us, “there was a concern” on the part of the reviewers that she had not proposed to collect specimens that would enable her to measure, for example, biomarkers of nutrient levels in the blood. This prompted her to consider: “I was actually going to call the program officer … to say, ‘Are you going to fund a study that doesn’t have any biospecimens? Just tell me now. And I won’t waste my time.’” Biospecimen collection, in this scientist’s view, had come to be predictably demanded by grant and journal reviewers and perceived as a marker of robust science:

> There was a perception in the field that some of the senior scientists, you know, don’t like self-reported data. And they think, yes, you need to go into the body. You need to measure the nutrient level in the body… It was a convergence of that school of thought … and also a laboratory technology innovation that allowed these things [such as measures of nutrient levels in blood specimens] to be done more cheaply.

This participant described a current study investigating interactions between genetic markers of risk and nutrient levels in the blood and the effects of nutrient supplementation on gene expression. For her, this study exemplified her observation that most grants awarded for the study of diet, exercise, and cancer risk now incorporate “something that’s endogenously measured” in the body. Indeed, she told us that it would be hard to imagine that any project would be funded without proposing to collect a simple and cheap specimen — such as saliva from a spit cup — to enable future molecular or genetic analyses. This scientist seemed to concede that the drive to collect and analyze nutrient levels in the body, even if only in response to feedback from reviewers and colleagues, “really solidifies the ground you stand on” by illuminating the molecular biology behind health outcomes in making lifestyle recommendations.

As these scientists defined the ‘environment’ in terms of what it was not — genetic risk — they justified the inclusion of bodily attributes, processes, and behaviors as ‘environmental’ contexts thought to modify or interact with genetic risk. They understood clearly attributes such as obesity, hypertension, parity, and diet as the product of complex social dynamics that found their way eventually into the body. The body itself then became re-cast as an environmental context modifying molecular and genetic processes occurring within it. These scientists thus created an epistemic hinge connecting all manner of complex behaviors and determinants to bodily attributes (e.g. BMI, physical activity) and physiological processes of bodies (e.g., hormone metabolism and blood pressure). Along the way, bodies and biospecimens became the most credible source of knowledge of the environment, and traditional epidemiological self-reported data was seen as increasingly suspect.

However, some of our participants expressed some ambivalence and even skepticism of the ultimate value of ‘going into the body.’ The researcher studying diet and cancer quoted above, for example, qualified her own compliance with this demand to get down to the molecular mechanism:

> At the same time, I really wear a different hat at different times. Sometimes I think, well look, you know exercising and not being obese, I don’t necessarily have to know everything about the biology behind that and how it’s affecting your tumor to make that recommendation. I have sort of that tension in my own mind about it.

Similarly, a leading cardiovascular disease researcher we interviewed expressed both deep scientific curiosity in GEI research but alongside it a passion for population-level disease prevention. When asked to reflect on whether she saw the former contributing to the latter, she answered:

> I think eventually. Right now being a genetic epidemiologist, [I have] really spent my last twenty years looking for these genes, and I know I feel [it's] scientifically very interesting to me. [But] when I look at the one billion people around the globe who have hypertension, I'm not sure that we can wait for the years and years it's going to take to discover all those important gene-environment interactions. We really have to start tackling the environment.

She went on to describe what she saw as more potentially impactful interventions, including policy changes such as lowering the guidelines for the sodium content of foods or improving the nutritional content of school lunches.

GEI researchers clearly felt subject to increasingly routinized demands to move their measures and etiological explanations deeper into the body. Yet in expressing their ambivalence and frustration, we saw that researchers did not always simply fall in line with these demands, but rather complicated and questioned the need for personalized and molecularized knowledge of the environment. In particular, they wondered about the public health relevance of identifying genes or gene-environment interactions when known interventions could effectively impact the environments scientists are seeking to molecularize and personalize.

Linking Internal and External Environments: Bodies Living in Environments

A second mode in which GEI researchers incorporated the environment was perhaps one of the most conventional: measuring how chemical and other exposures conventionally thought of as 'environmental' acted in joint and interactional ways with genetic variations. GEI researchers described expansive inventories and elaborate data collection strategies aimed at capturing the impact of human bodies living in environments suffused with chemical exposures and molecular assaults of all kinds. That is, aspects of the environment external to the body were understood to alter the internal physiological environments within bodies, in which human cells were immersed, that in turn were conceptualized to affect and interact with the DNA within those cells. Scientists we interviewed and observed reported collecting exhaustive data on polycyclic aromatic hydrocarbons from air sources, cleaning products and chemical agents found under participants' sinks, and dust samples from vacuum cleaner bags. They assessed geo-coded data on neighborhoods' distance to highways, and air and water quality measures from community monitoring stations. They asked their research subjects about occupational history and exposures. One genetic epidemiologist summarized such efforts as assessing a whole molecular environment of toxins that have until recently "been invisible to us."

But again, indicative of the strategy of moving toward the body to research the environment, our participants also told us that increasingly, they sensed that environmental exposure data based on external monitoring were deemed no longer sufficient. Instead, personal exposure measurements were seen as the best way to go. An NIH leader explained the perceived

limitations of community-level measures of environmental exposures through the example of a fictional child:

> But there has always been this question: … is the personal exposure to Joey playing [in] the playground characterized appropriately by the neighborhood monitor that might be three miles away from where Joey is, and how does that exposure change over time day to day? …Do those monitors really represent both current exposure, longitudinally selected exposed data, and does it predict future exposure?

Because of such concerns, our participants reported that exposures measured through a wearable air monitor, for example, or technologies for measuring biomarkers of exposure in biological specimens were increasingly routinized in epidemiological cohort studies.

One epidemiologist explained that the pressure he and his collaborators felt to make their research design and findings more convincing compelled them to incorporate personalized measures of air pollution to counter questions about whether they captured true exposures or effects:

> Our notion is that we've learned a lot about air pollution exposures [through air monitoring stations], but … that information hasn't been incorporated into epidemiology, for the most part. So we're trying to do it right in [our cohort study] … to answer critics who say, "Well, how can it be that you saw these relationships [between air pollution and disease risk]? [Did you] really measure what people were exposed to?"

He explained that to address this question, their current study included extraordinary efforts to measure and model air pollution *inside* research participants' homes, that is, closer to their individual bodies. Thus in contrast to external neighborhood or community-level data on pollution, their study gathered individual-level exposure data that could be analyzed alongside a genome-wide association study.

With these methods that move measurements closer to the bodies of research participants, GEI researchers created an epistemic hinge to link external physical, chemical environments to individual bodies and internal environments. In the NIH Genes, Environment, and Health Initiative, for example, NIH leaders promoted and invested in technologies for "personalized exposure assessment" (Weis et al., 2005). One GEI researcher described the initiative as "working in an engineering mode" to develop new tools for capturing a variety of environmental stressors in real time, including wearable sensors and monitoring technologies such as accelerometers and personal air samplers. By moving measurements closer to individual bodies and measuring biomarkers of exposure from biological specimens, researchers strategically responded to critics who demanded more precise measures at the individual level.

However, at times our participants regarded their practices with ambivalence, doubting the links that could be made between GEI science, personal measures of environmental exposures, and individualized health recommendations or "healthy" choices. One NIH leader explained that environmental assessment needed to "get personal" and molecular to keep up with emerging efforts to "personalize medicine." She speculated that "if people

know what they are exposed to," they might be able to act by calling Congress, or boycotting particular products perhaps. However, she then qualified her initial optimism for the potential for personal exposure assessment to instigate change: "Don't ask me how. I don't know how that happens." Other researchers questioned whether and how identifying genetic susceptibilities to particular chemicals (nutrients and toxins) or specific molecular mechanisms could yield better health recommendations.

Still others pointed to the limits of such individual recommendations to change environments. As one researcher told us, his study was "trying to exploit GEI relationships to understand the mechanisms of relationships between air pollution" and disease. He was motivated by the "idea that you're going to show that these genes are involved" in individuals' susceptibility and responses to pollution exposures. He conceded that "it's possible" to demonstrate such relationships. But he questioned the relevance of such information for public health given that "we're not gonna say that people who have a [genetic variant] … should all move away from big cities and out of the country," particularly since "people don't have as much choice as we would like [them] to." Yet, paradoxically, this GEI scientist also felt that data demonstrating the impact of environmental exposures on *genetic* mechanisms of disease provided more solid and persuasive evidence for the need for *societal*-level, policy changes to "improve the environment." Thus our participants linked genetic mechanisms and air pollution effects through an epistemic hinge, following the effects of physical, chemical, and environmental exposures into the body. Yet, in this move, they expressed uncertainty about whether and how this would significantly shift individual or collective possibilities for transforming health risks.

Embodying the Environment: Molecularizing Social Forces and Experiences?

Finally, the third mode in which GEI scientists enacted the environment in their research was by conceptualizing the environment as composed of social experiences that impacted bodies at a molecular level. They expressed deep appreciation of the ways bodies are embedded within and in turn embody ongoing social experiences and interactions through processes based in biology and molecular physiology. Our participants created an epistemic hinge linking complex social, environmental, and experiential phenomena to their impacts on physiologic processes potentially detected 'in the body,' and whenever possible, at the molecular level. These moves re-frame the body as a "molecular conduit" (Landecker & Panofsky, 2013) between social, environmental and biological complexity.

For example, at one scientific meeting, a researcher vividly painted a picture for the audience of the widening health disparities plaguing the large U.S city where she does her research: "I live [in a community] with all the poor people, like me. And this [indicating on a map] is where you have the rich people, and they just happen to be much more fair-skinned than I am, and they are on the white side." She then went on to discuss the potential causes of the health disparities, reflecting first on the maldistribution of and differential access to health care:

> And so, because of the segregation, you can imagine where all the doctors go to practice … Because the health profession is all about the business of medicine. So

> if you want to treat cancer, and if you want to get cancer diagnosed, you should live on the north side [of the city].

Her talk then downshifted from the business of medicine to biomarkers and molecular signals, as she described how social life can leave a "biological residue" that manifests in measurable biomarkers:

> People talk about how early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased pro-inflammatory signaling. People actually now have connected the social environment to biology … [The question is,] when is this happening? There's a lot that actually happens, and it's fixed before you ever get born … So the challenge is that we're seeing disparities because they start happening to minorities and poor populations by the time they get to us [in the clinic].

Thus evoking emerging hypotheses about the developmental origins of health and disease, she wondered about the impact of social life and "environmental stressors" on biology, and described biomarkers of inflammation or stress as the "biological residue" of embodied social processes. In so doing, she drew on her own experience living in a poor black neighborhood, and positioned embodied experience as an epistemic hinge integrating hypotheses about the social and biological origins of disease.

Other researchers similarly called on their *own* bodies, experiences, and identities to articulate the body as a site of translation between social and molecular processes. Beliefs, experiences, and perceptions understood as ephemeral or intangible were seen as materialized in bodily effects detected at the molecular level. For example, one researcher, a physician who was also trained in genetic epidemiology, told us that the findings of the Whitehall Study, the landmark study of British civil servants that linked occupational status to mortality (Marmot, 2003), even helped him re-conceptualize his own childhood experiences:

> I was fascinated by [the Whitehall Study] … It just fit like a hand in a glove with my childhood experiences. It was like an "Aha!" I didn't know how to verbalize what I'd experienced as a child, and Michael Marmot's work … allowed me the ability to verbalize it and conceptualize it … I am fascinated how social experience — you can't touch it, you can't weigh it, you can't measure it — but somehow that gets translated in our heads (or I'm assuming it's our head) … to a physiologic outcome.

He described being awakened to the possible translation of ephemeral social experience that "you can't touch" into "physiologic outcomes" that can be measured with biomarkers. His fascination with this process drew him to study allostatic load, or the physiological wear and tear caused by neural, endocrine, cardiovascular, and immunological responses to repeated and chronic exposures to stressors of all kinds. This prompted him to include in his study not only physiologic indicators, but also potential social determinants, of allostatic load that had been missing from previous genetic epidemiology studies he had conducted:

> It's like high blood pressure: high blood pressure leads to increased heart disease, kidney disease, both of which lead to premature death. So that's … what people

> call an allostatic load. Allostatic load can come from many different stresses. It can come from socioeconomic stresses, it can come from discrimination, it can come from gender discrimination. So I recognized that that was missing in my study.

Thus his research design now includes measures of acculturation, migration, and perceived discrimination, alongside measures of stress hormones, neuroendocrine responses, and other biomarkers produced by the kinds of physiological cascades such social processes are hypothesized to induce. In doing so, he positions the body as socially responsive and interprets 'the social environment' as manifest in molecular signals.

Another participant also used her own body to hypothesize how "people's beliefs are actually a strong biological context for genes to operate":

> What we believe and what we think actually plays deeply into the HPA axis [the stress response of the hypothalamic, the pituitary and adrenal systems] of how we respond to the world … So if I am a white woman in an African-American neighborhood and I have never had any exposure to African Americans except through the news, then I'm gonna have a belief system that probably charges my stress [response], my cortical system in a very different way than if I'm a white woman who grew up in a black neighborhood and actually have deep friend, family connections.

Speaking from her own position in the body of a "white woman," this researcher linked her understanding of how beliefs and experiences can be registered at the level of the body, to generalized and universal physiology of the cortisol system. She positioned "belief systems" as simultaneously personal, ephemeral, and objectively measureable, and linked them directly to the molecular physiology of the cortical system. She excitedly speculated about how personal beliefs form a "biological context" that naturalizes but also contextualized "how we respond to the world" in terms of stress hormones such as cortisol. Her molecularized treatment of embodiment highlighted a conversion of social processes into molecular effects, traces, and measures. In and through their excitement about embodying the environment, GEI researchers reduced social processes to bodies, and privileged biological and molecular mechanisms and sought to trace how various components get into the body.

Both conceptually and methodologically then, GEI scientists demonstrated a belief in what Margaret Lock calls "local biologies," defined as inseparably biological and social (Lock, 1993, 2013), or what Niewohner (2011) coined "customary biology." Niewohner used this latter term to capture how molecular biologists' excitement about new possibilities for incorporating 'social life' into their work "makes immediately plausible that even something seemingly hard-wired such as gene expression may be connected in significant ways to local cultural practices" (Niewohner, 2011, p. 293). Our researcher-participants sought to break these processes of translation into multiple knowable conversions, projecting social processes into physiological responses detected with biomarkers such as cortisol, ultimately reducing sociality to bodies. They proposed to study "the embodiment of the environment" with molecular techniques and thereby sought to quantify measures of the effects of social phenomena.

However, their enthusiasm about seeing the social environment ‘in the body’ was tempered by the challenges of conceptualizing, measuring, and modeling the social environment in accordance with their appreciation of its complexity. A geneticist working in large interdisciplinary collaborations recalled a conversation with a colleague who maligned social factors as “soft science.” The geneticist summarized some of her colleague’s concerns:

> You can measure the toxins in the air. You can figure out where the toxic waste dumps are and where they’re not. But it’s these other things — people’s perceptions, people’s mindsets, people’s experiences — that are the most challenging and that we tend to ignore because they’re so challenging. I can’t tell you how many times I hear people say, “But we can’t measure those. How do we measure those?”

Yet in itemizing these challenges, this participant seemed to almost tacitly agree that measuring “people’s perceptions, people’s mindsets, people’s experiences” and understanding their health effects were proving to be extraordinarily difficult. Nonetheless, she told us, “we need to figure out a way.” Thus our participants reported seeking out strategies to quantify, and make concrete measures of, “soft,” intangible, and fuzzy social experiences or unreliable self-reported data. So even as they questioned emerging mandates for precision and quantification (Ackerman, Darling, Lee, Hiatt, & Shim, 2016), the scientists we interviewed found that implicitly and explicitly, directly and indirectly, they were subject to escalating demands to more tangibly operationalize and ‘better’ measure social environmental risks.

Researchers also described encountering limitations and constraints that made it difficult to adequately and credibly substantiate the very complexity of the environment that seemed to them to be self-evident. Bemoaning the inability of post-genomic science to adequately grapple with complexity, for example, a genetic epidemiologist said: “Well, we’re like stone-age right now compared to what a real, good scientific model [of complexity] would be.” As she described it, current statistical and genomic methods are woefully inadequate: “The linear model … that we’re using [to do] statistically modeling is terrible for representing what the whole orchestration of the cell and the body and the tissues are really doing.” But new techniques offered fresh promise:

> It’s one of the reasons why the epigenetics studies right now have got people very excited, the idea of really at the molecular level, some kind of registering of the embodiment of the environment, the embodiment of a lifetime’s worth of experience moving with the genetic variation in a kind of concert and a kind of orchestra.

Our participants saw epigenetic techniques and studies of gene expression, along with new trans-disciplinary and interdisciplinary research, as holding particular promise to synthesize these complexities into a holistic view or synthetic perspective not yet possible within current research.

In short, we found that GEI researchers enacted, incorporated, and measured the environment in ways that often led them “into the body,” or at least closer to the body. But in

the face of imperatives to molecularize and personalize the environment in their research, they experienced ambivalence and frustration in working out exactly how to do so. Thus we found that the promises and effects of thinking and working molecularly were not straightforward for GEI researchers themselves.

Conclusion

In this paper, we presented the experiences and perspectives of GEI researchers working on the problem of gene-environment interactions and complex disease in the U.S. Examining shifts in GEI research at the level of NIH-led programs and in the current practices of NIH-funded researchers, we showed that while GEI researchers viewed the environment as almost 'anything non-genetic,' this conceptual elasticity yielded to imperatives to molecularize and personalize the environment. They often worked with the environment as if it could be translated into molecular biomarkers that could be measured in the body. Researchers encountered these imperatives from multiple sources, including NIH leadership and scientific reviewers, and saw them reflected in trends diffusing across biomedicine and post-genomic science. We cannot know for certain whether such trends are being driven by the NIH, or whether they reflect emergent standard practices in the life sciences more broadly. But it is clear that some epistemic hinges proved more durable and credible than others. By evoking a body responsive to, and continuous with, the physical and social world through its molecular physiology, GEI researchers articulated the body as a "molecular conduit" (Landecker & Panofsky, 2013) — a site of translation between that external environment and internal molecular physiology. In the process, bodies and environments were often conflated, bleeding into one another methodologically and conceptually, and the boundaries between the two were re-drawn.

Our participants' different strategies for creating epistemic hinges sought to simultaneously manage complexity across a causal spectrum, and deal with the ethics and politics of questions about who should be responsible for health risks. Despite post-genomic science's promises of precision, personalization, and the integration of 'biological' and 'social' knowledge, in practice, GEI researchers' appreciation of environmental complexity was mired with frustrations, ambiguities and practical constraints. Investigators' navigation of imperatives to molecularize reflected their own ambivalence about when and why molecular measures were needed, and how molecular knowledge would or should be put to use. GEI scientists in our study complicated the mandate to 'go into the body' by questioning what real world difference molecularized and personalized health recommendations could make, especially when compared to policy-level changes. Their ambivalence and struggles to create the environment as a 'doable problem' and fundable research question exposed the fissures, divides, and contradictions that effaced the synthesis of biological and social knowledge promised by gene-environment interaction.

GEI researchers' ambivalent responses to imperatives to molecularize provide an analytic and political opening for questioning the effects of thinking and working molecularly today. Our data show that making meaning of the 'environment' is an actively negotiated and unsettled matter. On the ground, the meanings and promises of molecular markers of risk and measures of the environment were not at all fixed. Researchers ascribe particular

qualities and ideals to molecular knowledge (e.g., seeing molecular knowledge as more personalized, more precise, or more integrative). Making links to molecular knowledge was critical in their efforts to incorporate the environment in their research. But they also experience molecularization in tandem with imperatives to personalize prevention and treatment, demands that some actively complicate and resist. Their experiences demonstrate the importance of understanding molecularization not only as ongoing transformations within biomedical science, but also as a set of unsettled and unsettling demands and imperatives that researchers negotiate and work through in their everyday contexts. We have shown how researchers engaged in the molecular world of post-genomic science actively question the implications of molecularization and the social or public health utility of molecularized or individual measures and personalized prevention recommendations.

What implications do these concepts and findings have for how we understand the causes of complex illnesses and health inequalities? For one, environmental exposures and genomic markers are no longer understood as competing explanations so much as interacting risk factors and concepts. Yet pushing credible explanations for health and illness upstream to social conditions and environmental contexts remains a key scientific question and political battle (Krieger, 2011). What social processes and power relations put people “at risk of risks” (Link & Phelan, 1995, p. 80)? What are the ‘causes of causes’ (Phelan et al., 2010)? These questions remain scientifically and ethically crucial.

Molecularization seems to stand as a ubiquitous and uncontested social process. Molecular techniques promise access to realities ‘invisible to us’ and provide answers to questions about what individuals should do to be healthy from deep ‘inside’ their bodies. For example, advocates of precision medicine seek to use molecular measures and techniques to fundamentally transform disease taxonomy and treatment (National Research Council of the National Academies, 2011). Similarly, we showed above how GEI researchers embraced speculation about the impact of society on biology in terms of knowledge of embodiment located in molecular processes; thus they re-articulated embodied knowledge and experiences into the language of molecular biology. In the process, research practices are re-shaping credible answers to questions about how social processes and inequalities ‘get under the skin.’ New possibilities for integrating genetic and social risk factors indicate a renewed investment in biological explanations that privilege “so-called basic processes in the body” at the expense of sociological studies, data and explanations (Duster, 2006, p. 10).

However, the social meanings of molecules within and beyond biomedicine are not by any means pre-defined, singular or stable. In attempting to manage causal complexity and causal accountability, GEI researchers are actively negotiating which kinds of epistemic hinges will be required to credibly link genes, bodies, and environments. Questions about who is responsible for health risks are at stake in these contestations. These findings should urge complex disease researchers across disciplines to unpack causal complexity through more diverse means. Will researchers continue to articulate epistemic hinges that narrow these possibilities, or enable epistemic openings that expand the methods that can produce credible knowledge of biosocial complexity? How can we widen spaces for openly discussing, and contesting, the rhetorical and methodological imperatives that shape what we can know and change about our environments?

As our findings show, the imperatives to molecularize and personalize may set new ethical responsibilities and choices for individuals, but they also open ambiguities and uncertainties for GEI researchers themselves. Rather than simply fueling molecularization, biomedical practices are both transforming and questioning what it means for human bodies to be made up of molecules. We cannot assume that molecular processes and knowledge offer a clear missing link between biology and society. Indeed, the social means and ends of molecular knowledge are precisely what GEI researchers grapple with and muddle through in their work. If we attend to these dynamics, social analysts and practitioners of post-genomic science alike may be afforded a more clear-eyed vision of the potentials and potential problems of efforts to produce fruitful and impactful representations of bodies, genomes, and environments.

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Research Highlights

- ‘The environment’ has shifting meanings in gene-environment interaction (GEI) science.
- Researchers navigate imperatives to molecularize and personalize the environment.
- Their “epistemic hinges” link environmental phenomena to biological and molecular processes.
- Post-Genomic research practices re-work the boundaries of bodies and environments.
- How we conceptualize the environment impacts who is responsible for health risks.