

Reconceptualizing and Defining Exposomics within Environmental Health: Expanding the Scope of Health Research

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BACKGROUND: Exposomics, the study of the exposome, is flourishing, but the field is not well defined. The term “exposome” refers to all environmental influences and associated biological responses throughout the lifespan. However, this definition is very similar to that of the term “environment”—the external elements and conditions that surround and affect the life and development of an organism. Consequently, the exposome seems to be nothing more than a synonym for the environment, and exposomics a synonym for environmental research. As a result, some have rebranded their “standard” environmental health research with the neologistic exposome term, whereas others ignore or seek to abandon the seemingly redundant concept of the exposome.

OBJECTIVES: We argue that exposomics needs to sharpen its mission focus to counteract this apparent redundancy. Exposomics should be defined as a research program in environmental health aimed at enabling a comprehensive and discovery-driven approach to identifying environmental determinants of human health. Similar to the aim of the Human Genome Project, exposomics aims to analyze the complete complexity of exposures and their corresponding biological responses. Exposomics’ primary premise is that the existence of undiscovered, potentially interconnected, nongenetic (environmental) risk factors for health necessitates a comprehensive discovery-driven analysis approach.

DISCUSSION: We argue that exposomics researchers should adopt our reconceptualization of exposomics and focus on the productiveness and integrity of their research program: its purpose and principles. We suggest that exposomics researchers should coordinate the writing of reviews that assess the program’s productiveness and integrity, as well as provide a platform for exposomics researchers to define their vision for the field. <https://doi.org/10.1289/EHP14509>

Introduction

Inspired by the Human Genome Project, C.P. Wild coined the term “exposome” to motivate the creation of improved exposure assessment and the discovery of mechanisms by which the body responds to exposures, innovations that are to be used for the pursuit of human health.^{1–3} Answering his proclamation, a flourishing community of exposome researchers successfully developed exposomics.⁴ These researchers have created novel analytic methodologies, new and improved exposure assessment tools and omics assays, and cohorts that integrate these advances through many large projects.^{5–28} As exposomics is maturing and gaining popularity, we set out to reflect on how exposome research is currently portrayed and used, in order to sharpen its mission focus.^{29–31}

Simply put, exposomics is not well defined. When we visit exposomics conferences and other related conferences, we hear this type of objection whispered, and there are indications of it in asides of various papers.^{32–37} At its best, such reasoning goes as follows. Exposomics is the study of the exposome.^{38–46} The exposome refers to all environmental influences and associated biological responses throughout one’s lifespan.⁴⁷ But is that not basically the same as the environment—the external elements and conditions that surround and affect the life and development of an

organism? Consequently, the exposome seems to be nothing more than a synonym for the environment, and exposomics a synonym for environmental health research. Even though this research approach flourishes, the exposome and exposomics seem to be redundant, nothing new, and mere neologisms.

It is our observation that, as a result of this objection, some people merely rebrand their environmental health research with the exposome term, without (fully) embracing its underlying innovative research plans.³⁷ This is an issue of mission creep because it dilutes the original purpose of exposomics. Partly *because of* such rebranding, we see that other researchers perceive the exposome and exposomics as unnecessary neologisms. To them, the exposome and exposomics seem redundant, and thus they ignore or seek to abandon the terms.

However, given the initial reasons for doing exposomics and its subsequent success, we argue that exposomics should be distinguished from other environmental health research, and thus needs to be further conceptualized and defined to preserve and enable its innovative potential.

There is a fundamental research premise that prompted the exposome concept, but which has not been explicitly thematized by previous research.^{1,25,28,48} Similar to the aim of the Human Genome Project to make possible the analysis of the entire genome’s complexity instead of taking a piecemeal approach,⁴⁹ exposomics aims to enable the analysis of the complete complexity of exposures and their corresponding biological responses as an alternative to taking a piecemeal approach. We hold that exposomics’ primary premise is that the existence of undiscovered, potentially interconnected, nongenetic (environmental) risk factors for health necessitates a comprehensive discovery-driven analysis approach. This premise signifies the intended value of the exposome concept next to that of the environment: to motivate and demarcate an approach to studying the *whole* complexity of exposures that affects health and disease.³

Due to the complexity of our environment, associated behaviors and lifestyles, and their potential interplay, it can be highly challenging to, in advance, fully define hypotheses that bear fruit. This challenge is akin to the history of genetic research, where many initial findings of low-penetrance candidate genes turned out

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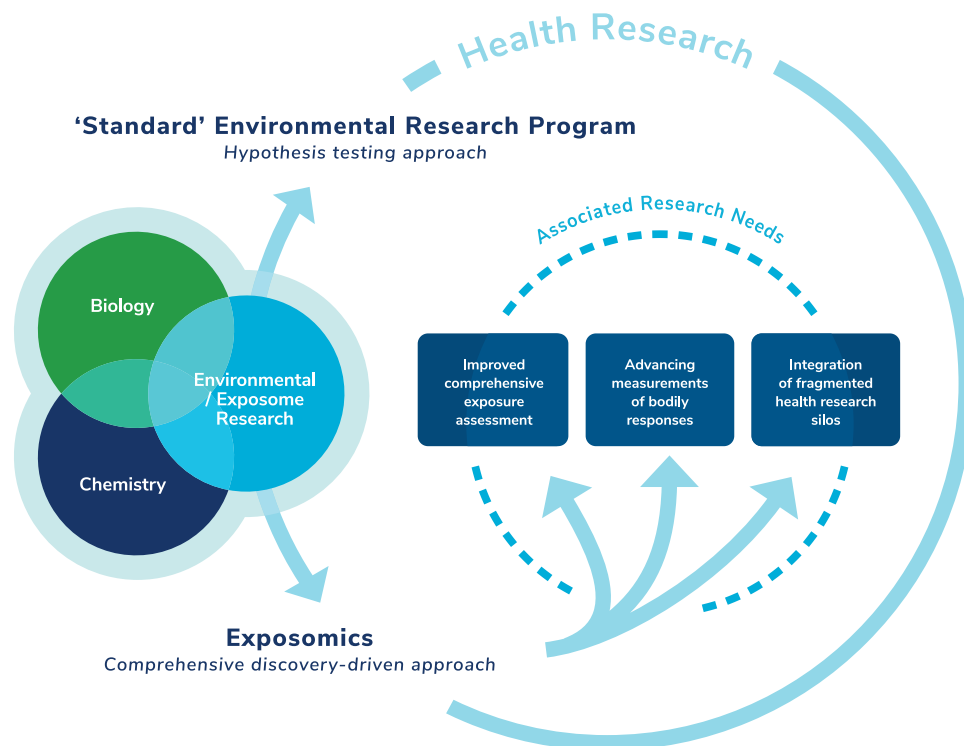


Figure 1. Exposomics in the scope of health research. In the circles on the left, environmental/exposome research is portrayed as a research area that, like chemistry and biology, investigates a “slice of reality” (e.g., all chemical compounds or all living entities). We define exposomics as a research program in environmental health aimed at enabling a comprehensive and discovery-driven approach to identifying environmental determinants of human health. The exposomics approach is distinctive yet complementary to the approach of the “standard” environmental research program that formulates and tests hypotheses. Both come together in the larger “Health Research” circle, given that both approaches feed into each other as aspects of human health research. Furthermore, to make possible a comprehensive discovery-driven approach, exposome researchers have specified three associated research needs, which we have indicated in the middle of the figure.

to be false positives.⁵⁰ However, comprehensive studies covering many genetic markers changed this situation, leading to robust and replicable genetic associations. Following this example, efforts in exposomics should be modeled on efforts in genomics to gather enough data and create the data analysis techniques required for genome-wide association studies (GWAS). Learning from these genomic efforts, we argue that one should think of exposomics as aiming to enable a comprehensive discovery-driven approach for health research on environmental factors.⁵¹

This approach does not replace hypothesis-driven research but, instead, offers a complementary approach to understanding the impact of our environment on health.⁵¹ Whereas a hypothesis-driven approach limits the number of environmental factors that will be analyzed per hypothesis, one general idea behind a discovery-driven approach is that

...there is a finite amount of data gatherable on a system, that a subset of that amount allows us to fully describe how the system works, and that the more of its superset we gather, the more relevant information statistical or [artificial intelligence]-based tools have for performing well and the less room exists for wrongfully omitting relevant variables.^{51(p74)}

Because we cannot continuously measure and analyze everything “nongenetic” in the universe, a discovery-driven approach to the whole environment should limit what is measured based on at least *a*) the capacity of measurement technology, and *b*) the requirements of data analytics (broadly construed). For instance, targeted vs. untargeted mass spectrometry involves a trade-off between sensitivity and coverage, and causal structure learning algorithms

require certain data assumptions to be met. As an operationalization of the environment, the concept of the exposome needs to be fit for the purpose of a discovery-driven approach to the whole environment.⁵² To make such an approach a reality, exposomics researchers formulated essentially three research needs: *a*) improved methods for comprehensive exposure assessment, *b*) the advancement of technologies to understand how the body responds to exposures, and *c*) the integration of fragmented health research silos that focus on particular categories of exposures or diseases instead of interconnected exposures or health outcomes.^{1,2,47,53}

In other words, to create everything that is required to enable discovery-driven research on the whole of the environment, exposomics researchers have effectively formulated a research program. In this respect, exposomics is not merely a research area that, like chemistry or biology, denotes the study of a “slice of reality,” such as all chemical compounds or all living entities. The term exposome also signifies the necessity of a systematic cognitive enterprise—as in genomics—to facilitate comprehensive discovery-driven research on the environment.³¹ Rappaport and Smith famously argued that “epidemiologists increasingly use GWAS to investigate diseases while relying on questionnaires to characterize ‘environmental exposures,’” even though “70 to 90% of disease risks are probably due to differences in environments.”^{53(p460)} Defining exposomics as merely the study of the environment, exposome, or a slice of reality, thus disregards the intended role of the exposome concept for advancing its research program within health research (Figure 1). Such a misunderstanding is understandable, however, given that it is inherent to the choice to coin a broadly defined neologism like “exposome.”⁵⁴ Because the definition of the exposome does not refer to a comprehensive discovery-driven approach, it is logical

that the term would be freely used by anyone studying environmental health.⁴⁷

Discussion

Moving Forward with Exposomics

Given the loose usage that the neologism “exposome” affords, those of us interested in making scientific progress in exposomics should answer the following questions: How can we best address misunderstandings about exposomics and maintain mission focus on enabling a comprehensive discovery-driven approach for health research? Can we retain the utility of the exposome concept for research, lest the concept be deemed redundant and its research program abandoned or dissolved through mission creep?² In other words, what is the best guidance to promote and develop the research program of exposomics?

To address these questions, we argue that exposomics researchers should actively adopt our proposed reconceptualization of exposomics into their automatized thinking about the field and the way that they introduce exposomics in articles and other communications. The thought pattern ‘exposome research, exposome, study of all exposures throughout the lifespan’ should be replaced by ‘exposomics, research program in environmental health, enabling comprehensive discovery-driven analysis.’ In addition, exposomics researchers should defend their research program against (arising) misunderstandings. In essence, exposomics researchers should focus on the productiveness and integrity of their research program—its purpose and principles.^{55,56}

The productiveness of exposomics requires clarity about its goals and material progress. Although the term “exposome” refers to an extremely large number of exposures and biomarkers, the ultimate goal of exposomics is not, and should not be, to exhaustively catalog the entire exposome as an end in itself.¹ Absent a medical tricorder from *Star Trek*, this is impossible.⁵⁷ It is also not cost effective to focus solely on creating measurement technology without integrating different data streams via systems biology and advanced data analytics. Instead, the plan should be to systematically *improve* our methods for reliable, comprehensive exposure–response assessment.^{18,28} Productiveness involves not merely understanding all of a person’s exposures but also how the body responds to those exposures. Making productive progress on this task is an iterative process that expands our measurement capability and knowledge base, and requires the reformulation, specification, or addition of research needs.^{58–60}

Whereas human DNA consists of a few entities that contain relatively static information that can be sequenced with a single technology, the exposome refers to an immense number of entities that differ widely between people and cannot be compiled with a single technology. Speaking of the exposome as something to be “sequenced” like the relatively static genome with a single DNA sequencer is therefore literally false and a misleading metaphor. The exposome needs to be compiled, not “sequenced.” As noted earlier, exposomics requires ever-better methods for compiling the data and creating the tools necessary for enabling a discovery-driven approach to the study of the complexity of the environment. In our view, productiveness focuses on exposomics researchers’ material progress in fulfilling the program’s research needs, adopting relevant developments outside of the exposomics field that may help it achieve its purpose, and creatively planning for what research will require in the future.

The integrity of the exposomics research program requires cohesion among research initiatives.^{55,56} Exposomics must retain its added value by remaining principally focused on the innovative fulfillment of its mission aim and the three research needs identified by its principals (see the middle of [Figure 1](#)). However, we

hold that its research program faces various pressures that illegitimately compromise its principles. As mentioned, the exposome concept currently affords misuse because it is not coupled to a comprehensive discovery-driven approach. Consequently, some researchers freely rebrand their research as exposome research while using only standard or conventional methods.³⁷ For instance, they concentrate on relating single exposures within exposure categories to disease, or, conversely, a single biological response to a single exposure or disease. Researchers claiming to perform an exposomics study should attempt to adhere to the discovery-driven approach of exposomics by gathering as comprehensively as possible (in technical and practical terms) exposures, biomarkers, and information about health to enable discovery-driven analyses.²⁸ We hold that deviations from the principles of exposomics for reasons of social pressure, bandwagoning, prestige, or reckless “inclusivity” can only have negative consequences for the program’s focus on enabling a comprehensive discovery-driven approach to health research.

We also hold that the integrity of the exposomics research program touches on a problem that has not yet been clearly identified. Because exposomics tools need to be developed iteratively, there exists the danger that they are developed within existing disciplinary boundaries instead of being integrated into an ever more comprehensive approach. At the same time, working with specific categories of exposures and biomarkers requires specialized knowledge, and there is a definite value in having a division of labor within exposomics.

Wild indicated as much when he specified different domains of the exposome: internal, specific external, and general external.² However, Miller warned of “exposome balkanization,” whereby researchers “bastardize” the exposome through adjectives.⁶¹ We think examples are “bisphenol A exposome” or “air exposome” and that such exposome divisions can be, but not necessarily are, instances of rebranding existing approaches. Dividing up the labor across components of the exposome is valuable for developing component-specific exposomics tools and methods. However, doing so runs counter to the exposomics research program if its discovery-driven approach is not adopted or if there is no plan for integrating such tools into general strategies for comprehensive exposure assessment. The importance of such research integration needs to be actively pursued by exposomics researchers, and there is no easy shortcut for this commitment. To keep it present conceptually, it would perhaps be better to think and write of *components* of the exposome, such as the “air component of the exposome” rather than the “air exposome.” Nevertheless, such a phrase is not economical and can be cumbersome, in, for example, a paper title or section heading. Concepts can always be misused, and at some point we simply must remember that “the price of objectivity is eternal vigilance.”^{62(p509)}

That said, we do hold that exposomics researchers need to explicitly think about how to best leverage the division of labor while maintaining the comprehensiveness of exposomics when setting up research projects. The Human Genome Project faced a similar but less thorny issue when dividing up the work, since the nuclear genome consists of separate chromosomes that contain a similar type of information. To protect the comprehensive aims of exposomics, we hold that integrity requires the specification of research program-wide plans to *a)* leverage a division of labor, *b)* integrate fragmented research silos, and *c)* retain focus on discovery-driven analyses across strata of exposures and biomarkers. The recent establishment of the International Human Exposome Network may provide such a platform to start talking about coordination and division of work.⁶³

How can exposomics researchers best promote the research program view of exposomics? Although there have already been a

number of reviews of exposomics, we suggest that researchers who lead exposomics projects should coordinate the writing of a new type of review that analyzes, assesses, and guides the program's productiveness and integrity. Given exposomics' potential for mission creep, these reviews should analyze the field of exposomics to purposefully guide its research program toward its mission of enabling a comprehensive discovery-driven approach. First, the reviews should emphasize the added value of a comprehensive discovery-driven approach to the study of health and disease. Second, they should also provide a platform for exposomics researchers to define their vision for exposomics and to identify relevant developments outside of exposomics. Third, these reviews should serve as a comprehensive record of exposomics, unifying disparate publications, and enabling funding agencies and non-exposomics researchers to assess its progress globally in an accountable way that can guard against overpromising.^{55,57}

With such an eye to the future, let us reflect on how discovery-driven research relates to hypothesis-driven research. As we mentioned and visualized with the health research circle in Figure 1, discovery-driven research is an additional investigative pathway that feeds into hypothesis-driven research (and vice versa) and does not invalidate existing knowledge about health.^{25,64} In practical terms, new hypotheses that are brought forward by discovery-driven research should be followed up by hypothesis-testing research through a variety of research tools and designs (such as triangulation of evidence).^{15,18} Conversely, existing knowledge on environment-health associations should be considered in discovery-driven analyses through, for example, explicit priors.^{51,64} However, with the development of ever more expansive theories about mechanisms of exposure–biomarker–disease pathways, there will be an increasing number of hybrid approaches that combine discovery-driven and theory-driven elements. A good example of a hybrid approach is the semi-agnostic method(s) of “functional exposomics.”^{28,65} Since genomics has moved away from purely agnostic to functional genomics, this may also be the natural path that exposomics will take.

Conclusion

We return to our original question: If exposomics indicates the comprehensive and discovery-driven study of environmental health, then what is the added value of the exposome concept next to the concept of the environment? To answer this question, we need to start by distinguishing the exposome *from* exposomics. Suppose, as we have argued, that exposomics is primarily a research program that studies the comprehensive impact of the environment on health via a discovery-driven approach. In that case, exposomics should not be distinguished with a synonym of the environment (the exposome) from other environmental health research. Instead, exposomics needs to be defined in a way that distinguishes it from noncomprehensive and hypothesis-driven environmental health research. Therefore, we define exposomics as a research program in environmental health aimed at enabling a comprehensive and discovery-driven approach to identifying environmental determinants of human health.

With this distinction between different types of research approaches in place, we now need to note that operationalizations of the environment differ strongly depending on one's research aim(s), and often cause discussion and confusion.^{37,66,67} This is where the added value of the exposome concept next to that of the environment can be found: to demarcate *the way in which* exposomics studies the environment, as opposed to how other approaches study the environment. If there is value to be found in this neologism, we hold that the exposome concept should serve to operationalize the complexity of the environment and associated biological responses in such a way as to enable a comprehensive discovery-driven path to

understanding human health. As we have argued above, such an operationalization includes (among others) limits based on *a*) the capacity of measurement technology and *b*) the requirements of data analytics, but it also includes an extension of the “environment” to encompass part of the body's internal chemical products.⁵³ In other words, the exposome concept should serve the mission of exposomics, not vice versa.^{28,51} Naturally, there is more to be said (and should be said) on *how* the exposome can best be fit for its purpose (and how a good definition of the concept should reflect this fact); our point here is that the utility of the exposome should be a function of the exposomics research program.

To summarize, by reconceptualizing what exposomics is about, we have defended the value of the exposome and exposomics concepts from objections that equate the exposome with the environment and exposomics with the study of the exposome; objections which cause mission creep for exposomics as a research program. The next step for the field is to ensure that the mission of exposomics is keenly focused on advancing our understanding of the *whole* complexity of the environment and its biological effects on human health and disease.

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