Environmental Science & Technology

pubs.acs.org/est

Viewpoint

Exposomics Crosses the Rubicon: Let the Building Begin

Published as part of Environmental Science & Technology special issue "60th Anniversary of Environmental Science and Technology".

Gary W. Miller,* Rima Habre, and Chirag J. Patel

Cite This: *Environ. Sci. Technol.* 2026, 60, 13245−13248

Read Online

ACCESS | Metrics & More | Article Recommendations

KEYWORDS: *Human Genome Project, exposomics, human exposome*

A basic tenet of biology is that the human phenotype results from a combination of our genes and environment. Identifying the relative amount of genetic and environmental influences and the molecular basis of these traits requires considerable effort. On the genomic side, we had the Human Genome Project. It was a remarkable achievement characterized by collaboration, competition, intrigue, and drama. It provided the first map of the human genome and spurred a litany of scientific and medical advances. It may not have lived up to the hype of explaining the majority of disease risk, but the reality was that we already knew from heritability studies that our genes could only take us so far.

The leaders of the Human Genome Project devoted their lives to uncovering the mysteries of the genes. Just like Antonie van Leeuwenhoek's microscope to see tissues at a cellular level or Galileo Galilei' new telescope to see the stars with unprecedented resolution, in the early 2000s, genetics finally had the tools to systematically measure the genetic code. Not unexpectedly, a decade after, many scientists went into a genetic frenzy, and these exciting genetic-based approaches, such as high-throughput sequencing and genome-wide association studies, changed the paradigm for genomic discovery and research and, as a result, biomedicine for years. We have seen the cost of personal sequencing plummet and witnessed routine genetic testing and genomics be integrated into medicine.

The incredible success of genomics, though, has led to somewhat of an ironic and inconvenient reality. Our genes cannot explain it all. Indeed, for most chronic human diseases, such as heart disease, Type 2 diabetes, and chronic renal disease, genetics can only explain a minority of disease variability. There is still work to be done in genomics. We need to understand the distribution of genetic variants in different populations and to identify the missing inheritance. The missing inheritance problem, though, pales in comparison to the *missing noninheritance problem*. The amount of unexplained nongenetic variability in human disease is vast and represents a grand vista of discovery, ultimately telling us about how those genes function.

Cue the exposome. The environmental complement to the genome is the exposome—the integrated compilation of the physical, chemical, biological, and social factors that impact biology and health.[1] Exposomics provides the most comprehensive approach available to capture the complexity of the environment and permit integration of the environment and genes when studying human health and disease, leaving room for the stochastic nature of the underlying processes. We are now poised to perform exposome-wide association studies (ExWAS)—or studies that can scan the thousands of environmental and social exposures one experiences over a lifetime and how they impact disease risk—at an unprecedented level of resolution.[2−4] We can measure thousands of molecules by mass spectrometry in biospecimens and map people's place-based exposures over space and time with incredible accuracy[5] (Figure 1). Exposomics should lead to the identification of more true associations between the environment and health. Yet, the study of environmental contributions to health and disease should not occur in isolation. This is an exciting opportunity to use what we have learned about specific genetic linkages to human disease to serve as a template for how to study the impact of environmental exposures; e.g., mutations in a genetic pathway may explain 10% of disease variation, but that same pathway may also be targeted by environmental factors that, together, explain a much higher percentage of that disease. Conversely, for known environmental causes of disease, genetics can help to explain the range of vulnerability to that factor within the population. It is not genes OR environment but rather genes AND environment.

The recent advances in exposomics, including harmonization of mass spectrometry methods, increased application of geospatial sciences for reconstructing place-based environ-

Published: May 1, 2026

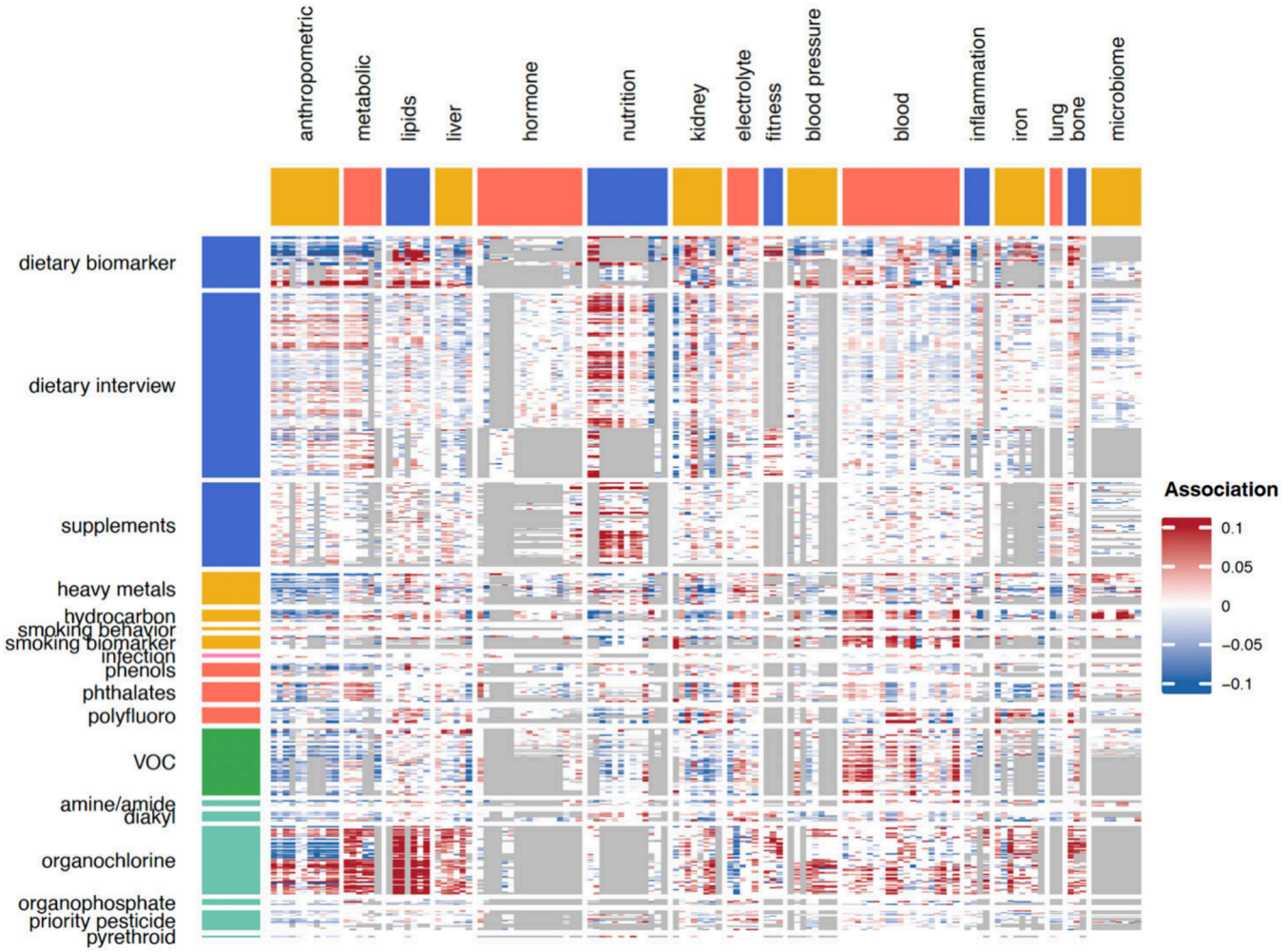

Figure 1. ExWAS map. This figure shows a representative ExWAS map across ∼300 phenotypes, with each pixel showing the direction of the effect. Data from analytical chemistry, dietary inventories, and self-reported lifestyle factors can all be integrated into the ExWAS, which can be expanded as higher-resolution measurements are obtained.

mental exposure histories, and improvements in privacy-preserving data systems and computational approaches, provide compelling evidence that exposomics has arrived—we have crossed the Rubicon. The apocryphal story of Julius Caeser indicates that he stated "Alea iacta est" (the die is cast) when he crossed the Rubicon River, representing going past the point of no return. He was warned that crossing the Rubicon River would be viewed as an act of war. This meant civil war, the establishment of the Roman Empire, and an influential yet relatively short reign that ultimately ended in his demise, but there was no turning back.

Fortunately, exposomics will not suffer that same fate. By working closely with colleagues in other fields in a collegial and collaborative manner, exposomics can learn from other disciplines and build synergistic partnerships. Scientists in the fields of genomics and exposomics are not adversaries, and the disciplines should not be siloed. The goal of investigators in both fields is to better understand the drivers of human disease and biology. Ideally, that knowledge is used to prevent disease and optimize health and wellbeing. Genomics and exposomics complement one another, and both are needed, but exposomics needs some nurturing to become an equal partner with genomics.

Now that we have crossed this proverbial threshold, it is time to build exposomics as a unique discipline. The foundation for this structure is the undeniable role of the environment in human disease, and we propose that there are four major walls required for this structure to withstand the onslaught of data and to deliver knowledge and inform action.

(1) We must commit to continually improving our ability to *measure* and *model* all facets of our environment. Measurement science requires improved and standardized sampling protocols and analysis techniques (e.g., mass spectrometry, nuclear magnetic resonance, etc.), constantly improving detection limits and knowledge bases to enable accurate identification and quantification of environmental exposures in biospecimens and in environmental media. Sensing innovations span geostationary satellites to personal sensors and wearables, with miniaturized detectors, microfluidics, and quantum sensing constantly pushing the envelope. Measurements, however, are exponentially more powerful when integrated with process-based models of the environment, human behavior, exposure, and internal dose. The innovation must be unrelenting.

(2) We must develop *databases* that retain the richness of exposomics data while preserving privacy requirements and enabling multiuser authentication and federated analysis.

https://doi.org/10.1021/acs.est.6c02721
Environ. Sci. Technol. 2026, 60, 13245−13248

Databases span predicted surfaces of environmental exposures (e.g., air pollution) or social exposome factors (e.g., migration and poverty), to biobanks and laboratory-based assay data (measurements), clinical and cohort data (electronic medical records, questionnaires, and health assessments), and phenotypes. These will need to be dedicated for exposomics so that they can be fit the purpose. Common data and metadata standards and mapping to ontologies and knowledge graphs are essential to enable intraoperability, data harmonization, machine readability, i.e., artificial intelligence ready, and discovery.

(3) We must develop *interoperability* workflows and systems that allow exposomics data to be seamlessly integrated with other types of data, such as electronic health records, claims data, imaging data, genomics, and proteomics for large-scale analysis. This requires careful integration across space, place, and time and consideration of appropriate methods for linkages between the environment, humans (meaning exposure), and health. It also requires big data-computed platforms, systematic methods that protect against false discovery, and techniques that require or enable reproducibility.

(4) We must develop the tools that allow the transference of *data to knowledge*—of upstream causes, effective interventions, and policy levers. This is not a mere intellectual exercise. We must deliver knowledge that can be used by policy makers, clinicians, consumers, and industries to improve human health and minimize the burden of disease.

The walls are not intended to be barriers to outsiders. They merely provide a home and an address for this critical field. The walls create a structure that will allow scientists to explore the connections between the environment and human health and to create useable information for those in other fields to make the connections. If built to proper specifications, these walls should be able to support monumental growth.

Exposomics has crossed the Rubicon River in search of collaboration, and we can confidently state that exposomics is past the point of no return. We are now revealing insights into human health and disease that cannot and should not be ignored.[2] Given the current state of the science, exposomics can deliver an -omic scale analysis of the environment and its impact on health. It is time to build the infrastructure to support exposomics and pursue efforts at the scale of the Human Genome Project. There is no turning back.

AUTHOR INFORMATION

Corresponding Author

Gary W. Miller − *Department of Environmental Health Sciences, Center for Innovative Exposomics, Columbia University, New York, New York 10032, United States;* orcid.org/0000-0001-8984-1284; Email: gary.miller@columbia.edu

Authors

Rima Habre − *Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, United States*

Chirag J. Patel − *Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts 02115, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.6c02721

Notes

The authors declare no competing financial interest.

Biography

Dr. Miller serves as Vice Dean for Research Strategy and Innovation, Adrienne Block Professor of Environmental Health Sciences, Professor of Molecular Pharmacology and Therapeutics, and Director of the Center for Innovative Exposomics. Dr. Miller is a leader in the field of exposomics, which studies the comprehensive and cumulative effects of physical, chemical, biological, and social factors that influence biology and health. His laboratory uses exposomics to study the environmental drivers of neurodegeneration. His team has successfully used high-resolution mass spectrometry in a variety of models (mice, rats, *Caenorhabditis elegans*, zebrafish, *Drosophila*, killifish, and *Planaria*) and biological samples (plasma, serum, cerebrospinal fluid, bile, interstitial fluid, brain, liver, lung, and lymph nodes). Dr. Miller is a Fellow of the American Association for the Advancement of Science and serves on the advisory panel of the National Institutes of Health *All of Us* Research Program. In 2026, he will serve as an International Collen-Francqui Chair at Ghent University, Antwerp University, University of Liège, KU Leuven, and Hasselt University in Belgium. Dr. Miller is the lead investigator on the NIH-supported NEXUS Exposome Coordinating Center and the APRA-H-funded IndiPHARM project.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health Grant U24ES036819.

REFERENCES

(1) Miller, G. W.; Bennett, L. M.; Balshaw, D.; Barouki, R.; Bhutani, G.; Dolinoy, D.; Gao, P.; Jett, D.; Karagas, M.; Klanova, J.; Lein, P.; Li, S.; Metz, T. O.; Patel, C. J.; Pollitt, K.; Rajasekar, A.; Sille, F.; Thessen, A.; Thuault-Restituito, S.; Vermeulen, R.; Ward-Caviness, C. K.; Wright, R. Integrating exposomics into biomedicine. *Science* **2025**, *388* (6745), 356−358.

(2) Patel, C. J.; Ioannidis, J. P. A.; Manrai, A. K. An atlas of exposome−phenome associations in health and disease risk. *Nat. Med.* **2026**, *32*, 1501.

(3) Chung, M. K.; House, J. S; Akhtari, F. S; Makris, K. C; Langston, M. A; Islam, K. T.; Holmes, P.; Chadeau-Hyam, M.; Smirnov, A. I; Du, X.; Thessen, A. E; Cui, Y.; Zhang, K.; Manrai, A. K; Motsinger-Reif, A.; Patel, C. J; Adamu, Y.; Adebamowo, C.; Akhtari, F.; Akhtari, F.; Argos, M.; Arunachalam, S.; Baumert, B.; Beglarian, E.; Berger, K.; Bhutani, J.; Bisson, W.; Breton, C.; Cai, L.; Chao, M.-r.; Chatziioannou, A. C.; Cheng, Q.; Chung, M. K.; Chung, M. K.; Chung, M. K.; Clark, R.; Cohen Hubal, E.; Conti, D.; Cooke, M.; Costello, E.; Cui, Y.; Dierickx, E.; Dolinoy, D.; Du, X.; Engel, L.; Gao, P.; Gaulke, C.; Giebelhaus, R. T; Goodrich, J.; Grafanaki, K.;

Gullapalli, R.; Habre, R.; Haidari, A.; Harari, H.; Hart, J.; He, J.; Holmes, P.; Hood, D. B; House, J.; Hu, H.; Hu, C.-w.; James, P.; Jankowska, M.; Ji, H.; Srimathi, K.; Konstantinou, C.; Lai, Y.; Langston, M.; Lasalle, J.; Leang, A.; Liang, D.; Liao, J.; Luo, J.; Makris, K. C; Manz, K.; Miller, G.; Motsinger-Reif, A.; Ouidir, M.; Page, G.; Pan, S.; Parker, G.; Paul, K.; Peluso, A.; Penning, T.; Pierce, B.; Prajapati, N.; Prins, G.; Quintana, P. J E; Rajasekar, A.; Ramesh, A.; Ruden, D.; Rushing, B.; Scholl, E.; Schussler-Fiorenza Rose, S. M.; Shah, R.; Shahriar, M.; Siwakoti, R.; Soares, L.; Soliman, G.; States, J C.; Stingone, J.; Sturla Irizarry, S.; Sun, Y.; Sundseth, S.; Teitelbaum, S.; Thessen, A.; Tong, A. P.; Vijayakumar, N.; Walker, R.; Wang, Y.; Whyte, K.; Wilson, A.; Wu, L.; Wu, K L.; Yuan, X. j.; Zhang, Q.; Zhang, X.; Zhao, N.; Zhu, Y. Decoding the exposome: data science methodologies and implications in exposome-wide association studies (ExWASs). *Exposome* **2024**, *4* (1), osae001.

(4) Patel, C. J.; Ioannidis, J. P. Studying the elusive environment in large scale. *JAMA* **2014**, *311* (21), 2173−4.

(5) Lai, Y.; Koelmel, J. P.; Walker, D. I.; Price, E. J.; Papazian, S.; Manz, K. E.; Castilla-Fernández, D.; Bowden, J. A.; Nikiforov, V.; David, A.; Bessonneau, V.; Amer, B.; Seethapathy, S.; Hu, X.; Lin, E. Z.; Jbebli, A.; McNeil, B. R.; Barupal, D.; Cerasa, M.; Xie, H.; Kalia, V.; Nandakumar, R.; Singh, R.; Tian, Z.; Gao, P.; Zhao, Y.; Froment, J.; Rostkowski, P.; Dubey, S.; Coufalíková, K.; Seličová, H.; Hecht, H.; Liu, S.; Udhani, H. H.; Restituito, S.; Tchou-Wong, K. M.; Lu, K.; Martin, J. W.; Warth, B.; Godri Pollitt, K. J.; Klánová, J.; Fiehn, O.; Metz, T. O.; Pennell, K. D.; Jones, D. P.; Miller, G. W. High-resolution mass spectrometry for human exposomics: expanding chemical space coverage. *Environ. Sci. Technol.* **2024**, *58* (29), 12784−12822.

https://doi.org/10.1021/acs.est.6c02721
Environ. Sci. Technol. 2026, 60, 13245−13248