The Exposome Paradigm in Human Health: Lessons from the Emory Exposome Summer Course

Megan M. Niedzwiecki and Gary W. Miller
Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

SUMMARY: The environment plays a major role in human health, yet tools to study the health impacts of complex environmental exposures are lacking. In 2005, Christopher Wild introduced the concept of the exposome, which encompasses environmental exposures and concomitant biological responses throughout the life course. Exposome-based approaches have the potential to enable novel insights into numerous research questions in environmental health sciences. To promote and develop the concept of the exposome, the Health and Exposome Research Center: Understanding Lifetime Exposures (HERCULES) Exposome Research Center at Emory University held the first Emory Exposome Summer Course from 13–17 June 2016. https://doi.org/10.1289/EHP1712

Introduction
For human health, exposures matter. A recent analysis of 28 chronic diseases in monozygotic twins found that the proportions of disease risks attributable to genetics were modest, with genetic population-attributable fractions ranging from 3% to 49% and a median of only 19% (Rappaport 2016). Beyond disease, the largest meta-analysis of twin studies to date estimated that across all complex traits, the influences of genetic (G) and environmental (E) factors are nearly equal (Polderman et al. 2015). Nevertheless, great efforts have been made to sequence and understand the genome—namely, the Human Genome Project (Lander et al. 2001) was successful in unraveling many mysteries of our genetic code—whereas few tools are available for comparable efforts in exposure science.

The “exposome,” a concept that encompasses environmental exposures and concomitant biological responses throughout the life course, was first proposed by Christopher Wild in 2005 to raise awareness of the importance of comprehensive exposure assessment in human health research (Wild 2005). This definition includes all exogenous and endogenous environmental influences—spanning environmental pollutants, diet, infections, radiation, social and psychological factors, the built environment, climate, and internally derived factors from inflammation, oxidative stress, and the microbiome (Miller 2014; Miller and Jones 2014; Wild 2012)—and the biological responses to these exposures (Miller and Jones 2014). In environmental health sciences, the exposome paradigm represents a necessary shift from a targeted, hypothesis-driven approach toward a broader, yet complementary, discovery-based model.

An exposome-based approach would benefit many research questions in environmental health sciences. Environmental exposures do not exist in isolation, and a thorough understanding of the interactions among the internal and external components of the exposome would be a monumental advance in the All of Us Research Program, formerly known as the Precision Medicine Initiative® (Collins and Varmus 2015; Leppert and Patel, 2016).

It is time that the exposome receives the thorough investigation it deserves, but how should we approach this task? How can the concept of the Human Exposome Project, a proposed environmental analog to the Human Genome Project, be realized? Compared with the genome, the dynamic and variable nature of the exposome renders its characterization far more complex.

At the Health and Exposome Research Center: Understanding Lifetime Exposures (HERCULES) Exposome Research Center, the first exposome-based P30 Core Center funded by the National Institutes of Health, we are beginning to address these questions. Researchers from departments across Emory University and Georgia Institute of Technology provide core services in data sciences, high-resolution untargeted metabolomics, targeted exposure analysis, and clinical/population research services for exposome-related research. We have three main goals for HERCULES: first, to promote the concept of the exposome; second, to develop the underlying tools necessary to study the exposome; and third, to disseminate the exposome concept to the broader research community by providing the means for nonenvironmental health scientists to incorporate the environment into their studies.

To introduce students to the concept of the exposome, several HERCULES researchers developed a two-credit “Genome, Exposome, and Health” course in 2013. Its success suggested to us that people outside of Emory could benefit from the content. We envisioned a larger course that would be open to researchers from all disciplines and locations and in which we could draw upon expertise from around the world. Thus, the Emory Exposome Summer Course was born.

The Emory Exposome Summer Course
From 13–17 June 2016, HERCULES hosted the Emory Exposome Summer Course. This was the first course of its kind on the exposome, with 150 attendees (130 paid registrants, 20 invited speakers) from seven countries and two dozen institutions. We used the course to promote the emerging concept of the exposome and to discuss approaches to advance the field. The week-long course featured lectures from top scientists from numerous disciplines, short talks by trainees, poster sessions, and computer-based laboratory sessions. We focused on illustrating the possible by engaging the students in hands-on activities. For example, following a didactic session on cloud computing, participants programmed the Raspberry Pi (www.raspberrypi.org), a $50 (U.S. dollars) handheld computer, to record real-time environmental data from their seats in the auditorium.

We found that the following four core principles were essential in the ultimate success of this course, and we recommend...
their adoption by others planning similar courses intended to foster research on the exposome and its usefulness in advancing environmental health.

**Gather a Diverse Team and Help Them Find a Common Language**

In the “$G \times E = \text{phenotype}$” paradigm, one of the variables ($G$) is represented by the field of genetics, a highly organized domain, and the other variable ($E$) is represented by a hodgepodge of disparate fields. The skills required to characterize $E$ necessitated that we reach outside our domain to gather a team from other research areas, institutions, and communities to capture all of the disciplines associated with studying the exposome. Because this course can serve as a model for others, we summarize both the core principles and the new tools with which to explore further as they emerged during this unique, interdisciplinary gathering (Table 1).

### Table 1. Invited speakers and topics from the Emory Exposome Summer Course.

| Disciplines               | Speaker                  | Institution                                      | Title                                                                 | Topic(s)                                                                 |
|---------------------------|--------------------------|--------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------|
| Environmental health      | David Balshaw            | National Institute of Environmental Health Sciences (NIEHS) | The Exposome at NIEHS                                                  | Emerging concepts and issues in implementing the exposome paradigm       |
|                           | Thomas Hartung           | Johns Hopkins University                          | Making Big Sense of Big Data on Little Chemicals                      | High-throughput toxicity screening; -omics; high-content imaging         |
|                           | Michael Jerrett          | University of California, Los Angeles            | Sensing the Exposome: Tales from the Tails of Distributions           | Key exposome concepts; comprehensive overview of external exposure monitoring |
|                           | Dean Jones               | Emory University                                 | High-Resolution Metabolomics as a Central Platform for Sequencing the Human Exposome | Untargeted metabolomics to monitor the internal exposome                |
|                           | Stephen Rappaport        | University of California, Berkeley               | The Exposome From Conception to Age 11                               | History of the exposome; EWAS strategies                                 |
|                           | Denis Sarigiannis        | Aristotle University of Thessaloniki             | The Exposome in Europe                                                | Overview of the Health and Environment-wide Associations Based on Large Population Surveys (HEALS) project |
| Translational sciences    | Christopher Austin       | National Center for Advancing Translational Sciences | Some Lessons for the Exposome From Previous “Big Biology” Projects    | Recommendations for exposome researchers from other large-scale projects |
| Engineering               | Kurt Pennell             | Tufts University                                 | Multiplexed Analyte Analysis                                          | Mass spectrometry methods for multiplexed exposure assessment           |
|                           | Douglas Walker           | Tufts University/Emory University                | Chemical Measurement by High-Resolution Metabolomics: Practical Considerations | Key concepts for the application of untargeted metabolomics             |
| Systems biology           | Alexandra Maertens       | Johns Hopkins University                          | Making Sense of Metabolomics Data with Networks and Multiomics Approaches | Overview of network analysis for metabolomics data                       |
|                           | Nicholas Stroustrup       | Harvard University                               | The C. elegans Lifespan Machine                                      | High-throughput screening to explore the role of the environment in the biology of aging |
|                           | Eberhard Voit            | Georgia Institute of Technology                  | Assessing the Exposome with Methods of Systems Biology               | Mathematical modeling strategies to understand the exposome             |
| Computational toxicology  | Allan Peter Davis        | North Carolina State University                  | The Comparative Toxicogenomics Database                              | Exposure data curation and integration                                   |
|                           | Cecilia Tan              | U.S. Environmental Protection Agency (EPA)       | Exposome Thinking at the EPA                                          | Exposome concept in risk assessment; high-throughput toxicity screening  |
|                           | John Wambaugh            | U.S. Environmental Protection Agency             | Playing With Data at EPA: ToxCast, ExpoCast, HTTK, and the Exposome    | High-throughput toxicity screening                                       |
| Bioinformatics            | Gari Clifford            | Georgia Institute of Technology                  | Playing in the Cloud with Exposomology (The Raspberry Pi 3 & A PIR Motion Detector) & Metabolomics Pathway Analysis and Integration | Demonstration of external exposure sensing with the Raspberry Pi         |
|                           | Shuzhao Li               | Emory University                                 | Metabolomics Pathway Analysis and Integration                        | Untargeted metabolomics pathway and network analysis                      |
|                           | Chirag Patel             | Harvard University                               | Data Analytics Approaches to Enable EWAS                             | Overview of EWAS strategies                                             |
|                           | Nam Pho                  | Harvard University                               | Demonstration of Cloud-Based, Data-Driven Exposome Associations with xwas and Rstudio | Demonstration of a cloud-based EWAS analysis                             |
| Computer science          | Karan Uppal              | Emory University                                 | Bioinformatics Tools for Metabolomics                               | Untargeted metabolomics data pre-processing and analysis                |
|                           | Sri Elaprolu             | Amazon Web Services                              | An Introduction to Amazon Web Services                               | Overview of cloud computing                                             |

Note: EWAS, exposome-wide association study; HTTK, high-throughput toxicokinetics.
Further, we posit that simply assembling an interdisciplinary team will be unsuccessful if the members lack effective methods of communication. Accordingly, we emphasize the need for unifying ontologies for exposome research. One such framework is the Exposure Science Ontology (ExO) proposed by Mattingly et al. (2012), which was developed based on the Gene Ontology project. ExO provides a standardized vocabulary for exposure science, with the goal of facilitating the integration of data from exposure science and other disciplines (Mattingly et al. 2012). Moreover, successful communication necessitates a forum enabling the free exchange of ideas, which we encouraged by structuring the course to include ample time for open discussion.

**Develop and Apply New and Better Monitoring Tools**

Monitoring the breadth of the exposome is not trivial. We must evaluate thousands of environmental stressors that not only vary by source, place, and time but also differentially affect individuals based on dose, route of contact, target tissue, and endogenous metabolic factors. What technologies are most promising for this task?

For example, our course included a demonstration of the Raspberry Pi, a new tool for external exposure monitoring. The Raspberry Pi, an inexpensive yet powerful handheld computer, can be used for on-site environmental monitoring. With the Raspberry Pi 3 and the Grove kit (Dexter Industries; www.dexterindustries.com/grovepi-starter-kit), a set of modular sensors, continuous home monitoring of temperature, humidity, air quality, dust, gas, and ambient noise can be conducted at an extremely low cost. In an interactive lab session, the ease with which the Raspberry Pi can be programmed to collect and store motion-sensing data became apparent. Although Raspberry Pi–based devices currently lack the sensitivity and reproducibility of traditional monitoring tools, their affordability and ease of use have the potential to enable their widespread adoption in all types of research environments, including secondary schools, and technological advances will improve the performance of these devices in the years to come.

Beyond the Raspberry Pi, there is a vast array of cutting-edge tools for monitoring external exposures, ranging from individual-level assessment with sensors, personal exposure monitors, imaging technologies, actigraphy meters, wristbands, smartphones, and data scraping algorithms to ecological-level assessments with satellite remote sensing, modeling, and geographical information systems. For internal biomonitoring, one full day of the course was devoted to metabolomics, a powerful technology to simultaneously detect environmental chemicals and biological responses in biofluids. We discussed an untargeted high-resolution metabolomics (HRM) workflow, which reliably measures thousands of environmental and dietary chemicals over seven orders of magnitude (subnanomolar to millimolar range) (Uppal et al. 2016). HRM provides a central reference platform to link exposure data, internal body burden, and the biological response to exposures (Jones 2016).

**Embrace Big Data**

Environmental monitoring tools enable the collection of terabytes of data. Now, how can we integrate this massive amount of information? And when we attempt to link exposures to phenotypes, how can we separate signals from noise?

Cloud computing services, such as Amazon Web Services (AWS), provide the storage space and computational power required to handle exposome-scale data. Cloud computing promotes the democratization of exposome research: it provides on-demand, high-performance computing solutions to researchers who lack access to these resources at their home institutions, with no upfront costs and with flexible pricing structures.

Exposome research is a team effort, but one practical challenge is the sharing and integration of Big Data. The course included discussion about how the Human Toxome Collaboratorium (Fasani et al. 2015) represents an excellent model for how heterogeneous, large-scale data can be synthesized and shared across institutions. The Collaboratorium is a shared computational environment that is hosted on AWS and in which data from consortium members or public domain data sets can be uploaded, analyzed, stored, and securely accessed by other members. The harmonization of exposome data also depends on standards for data reporting and metadata. Currently, the Children’s Health Exposure Analysis Resource (CHEAR) initiative from the National Institute of Environmental Health Sciences (NIEHS) is working toward the development of exposome data standards, which will promote exposome research collaborations in the broader environmental health community (Cui et al. 2016).

Sifting through a mountain of data to identify disease-related exposures requires advanced bioinformatics for data-driven discovery. One approach is the environment-wide association study (EWAS), which tests whether exposures within an exposome set are associated with a given phenotype. Accordingly, our course taught participants how to use the R package xwas (version 0.1; https://github.com/nampho2/xwas/) to link environmental exposures with aging phenotypes in National Health and Nutrition Examination Survey (NHANES) data (Patel et al. 2016), using RStudio (Rstudio) run through AWS. The course also demonstrated the value of EWAS strategies that involve the measurement of exposures using untargeted metabolomics, integration of exposome data with other -omics data, and identification of biomarkers with machine learning (Rappaport 2012).

For data-driven explorations of the predicted biological consequences of environmental exposures, one can take advantage of the wealth of information available through toxicology databases. Two notable examples are the Comparative Toxicogenomics Database (CTD), a comprehensive, curated database containing information on the interactions among chemicals, genes, diseases, and phenotypes (Davis et al. 2017), and the Toxin and Toxin-Target Database (T3DB), which contains detailed information on the chemical properties, targets, and toxic effects of thousands of chemical compounds (Wishart et al. 2015). For exposure predictions, the U.S. Environmental Protection Agency’s Toxicity Forecaster (ToxCast™), which contains the results of hundreds of high-throughput screens of thousands of chemicals, can be used to rank and prioritize chemicals using computational toxicology approaches (Richard et al. 2016). In addition to the rapid generation of exposure information, high-throughput screening methods, such as the Caenorhabditis elegans Lifespan Machine (which automates collection of C. elegans lifespan data) (Strousstrup et al. 2013), provide less costly, more humane alternatives to animal testing in vertebrates.

**Think “System”-atically**

To fully understand the interactions among the environmental and biological factors in the exposome, we must tackle this “paradigm of biological complexity” from a systems perspective.

Network theory offers an unsupervised, holistic approach to identifying disease-related components of the exposome. Networks are composed of “nodes” (e.g., environmental and/or biological metabolites, genes) that are connected by “links” (e.g., statistical correlations between nodes). Rather than investigating each exposure independently, one can study a network to find important nodes by identifying “hubs” (nodes with a large number
of links) and/or “cliques” (distinct clusters of related nodes) (Pavlopoulos et al. 2011).

Dynamical modeling, another promising method from systems biology, seeks to describe the temporal behavior of a complex system via mathematical relationships among the system components, typically using differential equations (Azeloglu and Iyengar 2015). For example, dynamical modeling has been used to predict the effects of pesticide exposures on dopamine metabolism (Qi et al. 2014). Although it is still in its infancy for multi-scale exposome tasks, dynamical modeling has the potential to enable major advances in personalized and predictive health.

Conclusions

The exposome concept was introduced in 2005, yet it remains in a quasi-primordial state. The Emory Exposome Summer Course was established to help advance the development of the exposome. Environmental health sciences is filled with untapped potential for human health discovery, and the exposome captures the excitement, the potential, and the dynamic nature of the field.

One important point that arose from the course is the need for academic researchers to include members of the community in exposome research. Participants discussed the need to promote citizen science, and the ethical considerations inherent in this endeavor, during an open discussion. For example, how can we engage with our communities to better understand the environmental health problems they face? Might improved exposure assessment lead to increased stigmatization of and discrimination toward at-risk communities (Coughlin and Dawson 2014)? Although not a focus of the course, these crucial questions are being discussed by other organizations, including the National Academies.

Another salient point that emerged from this course is the complexity of exposome projects that require long-term effort and considerable resources. Discussion at this meeting concluded that “staging” of projects and programs is essential. Staging involves defining measurable, incremental outcomes to assure all stakeholders that progress is being made and that the project remains worthwhile. We must agree on exposome “deliverables” and continue to publish reports describing the advancement of these goals.

Moving forward, it is essential to organize more opportunities for exposome researchers to share ideas, through both face-to-face meetings and online interactions. We plan to make the Emory Exposome Summer Course a recurring event (see emoryhercules.com/news/hercules-host-exposome-course-june-2016), and we encourage others in the exposome community to plan additional meetings and courses to promote exposome research. We hope that our four key recommendations will be useful for this task. Although a true exposome-scale analysis may not be feasible at present, embracing exposome-based approaches in environmental health research—and maintaining an open dialogue among stakeholders—will help move the Human Exposome Project from concept to reality.

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References

Azeloglu EU, Iyengar R. 2015. Good practices for building dynamical models in systems biology. Sci SignaI 8(88), PMID: 25852187, https://doi.org/10.1126/sci signal.aab8880.

Collins FS, Varmus H. 2015. A new initiative on precision medicine. N Engl J Med 372:793–795, PMID: 25635347, https://doi.org/10.1056/NEJMmp1500523.

Coughlin SS, Dawson A. 2014. Ethical, legal and social issues in exposomics: A call for research investment. Public Health Ethics 7:207–210, https://doi.org/10.1093/ phe/phu021.

Cui Y, Balshaw DM, Kwok RK, Thompson CL, Collman GW, Birnbaum LS. 2016. The exposome: Embracing the complexity for discovery in environmental health. Environ Health Perspect 124:A137–A140, PMID: 27479988, https://doi.org/10.1289/ ehp.1408412.

Davis AP, Grondin CJ, Johnson RJ, Scialy D, King BL, McMorrnan R, et al. 2017. The Comparative Toxicogenomics Database: Update 2017. Nucleic Acids Res 45:D972–D978, PMID: 27651457, https://doi.org/10.1093/nar/gkw838.

Fasani RA, Livi CB, Choudhury DR, Kleensang A, Bouhid M, Pendsse SN, et al. 2015. The human toxome collaborator: A shared environment for multi-omic computational collaboration within a consortium. Front Pharmacol 6:222, PMID: 26924963, https://doi.org/10.3389/fphar.2015.00322.

Jones DP. 2016. Sequencing the exposome: A call to action. Toxicol Rep 3:29–45, PMID: 28722641, https://doi.org/10.1016/j.toxrep.2015.11.009.

Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. 2001. Initial sequencing and analysis of the human genome. Nature 409:860–921, PMID: 11237011, https://doi.org/10.1038/35057062.

Leppert J, Patel C. 2016. Perspective: Beyond the genome. Nature 537:S105–S105, PMID: 27626778, https://doi.org/10.1038/537S105a.

Mattingly CJ, McKone E, Callahan MA, Blake JA, Hubal EA. 2012. Providing the missing link: The exposure science ontology ExO. Environ Sci Technol 46:3046–3053, PMID: 23224457, https://doi.org/10.1021/es2035857.

Miller GW. 2014. The Exposome: A Primer. Waltham, MA: Academic Press.

Miller GW, Jones DP. 2014. The nature of nurture: Refining the definition of the exposome. Toxicol Sci 137:1–2, PMID: 24213145, https://doi.org/10.1093/toxsci/kft251.

Patei CJ, Pho N, McDuffie M, Easton-Marks J, Kothari C, Kohane IS, et al. 2016. A database of human exposomes and phenomes from the US National Health and Nutrition Examination Survey. Sci Data 3:160086, PMID: 27779619, https://doi.org/10.1038/sdata.2016.96.

Pavlopoulos GA, Secrier M, Moschopoulos CN, Soldatos TG, Kossida S, Aerts J, et al. 2012. Providing the toxome: A call to action for aligning and connecting computational toxicology and chemical genomics datasets. Nucleic Acids Res 40:D1108–D1114, PMID: 22672124, https://doi.org/10.1093/nar/gkr893.

Rappaport SM. 2012. Biomarkers intersect with the exposome. Biomarkers 17:483–489, PMID: 22872124, https://doi.org/10.1080/1354750X.2012.691553.

Rappaport SM. 2016. Genetic factors are not the major causes of chronic diseases. PLoS One 11:e015437, PMID: 27105432, https://doi.org/10.1371/journal.pone.015437.

Richard AM, Judson RS, Houck KA, Grulke CM, Volarath P, Thillainadarajah I, et al. 2016. ToxCast chemical landscape: Paving the road to 21st century toxicology. Chem Res Toxicol 29:1225–1251, PMID: 27367298, https://doi.org/10.1021/acs. chemrestox.B600135.

Stroustrup N, Ulmschneider BE, Nash ZM, López Moyado IF, Ariefd J, Fontana W. 2013. The Caenorhabditis elegans lifespan machine. Nat Meth 10:665–670, PMID: 23668410, https://doi.org/10.1038/nmeth.2475.

Upmal K, Walker DJ, Liu K, Li S, Go YM, Jones DP. 2016. Computational metabolomics: A framework for the million metabolome. Chem Res Toxicol 29:1956–1975, PMID: 27629908, https://doi.org/10.1021/acs.chemrestox.B600179.

Wild CR. 2005. Complementing the genome with an “exposome”: The outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev 14:1847–1850, PMID: 16103423, https://doi.org/10.1158/1055-9965.EPI-05-0456.

Wild CR. 2012. The exposome: From concept to utility. Int J Epidemiol 41:24–32, PMID: 22296986, https://doi.org/10.1093/ije/dyr236.

Wishart D, Arndt D, Pon A, Jajed T, Guo AC, Djoumbou Y, et al. 2015. T3DB: The toxic exposome database. Nucleic Acids Res 43:D928–D934, PMID: 25378312, https://doi.org/10.1093/nar/gku1004.