

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

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**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 non-environmental 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](http://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

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

Discipline	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 Sarianni	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 Multi-omics Approaches	Overview of network analysis for metabolomics data
	Nicholas Stroustrup	Harvard University	The <i>C. elegans</i> 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, HHTK, 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)	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
	Karan Uppal	Emory University	Bioinformatics Tools for Metabolomics	Untargeted metabolomics data pre-processing and analysis
Computer science	Sri Elaprolu	Amazon Web Services	An Introduction to Amazon Web Services	Overview of cloud computing

Note: EWAS, exposome-wide association study; HHTK, high-throughput toxicokinetics.

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).

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](http://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) (Stroustrup 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](http://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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