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The Exposome: Molecules to Populations

Megan M. Niedzwiecki,[1] Douglas I. Walker,[1,2,3] Roel Vermeulen,[4,5,6] Marc Chadeau-Hyam,[4,6] Dean P. Jones,[3] and Gary W. Miller[2,7]

[1]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; email: megan.niedzwiecki@mssm.edu, Douglas.walker@mssm.edu

[2]Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia 30322, USA

[3]Clinical Biomarkers Laboratory, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Emory University, Atlanta, Georgia 30322, USA; email: dpjones@emory.edu

[4]Institute for Risk Assessment Sciences, Utrecht University, 3584 CM Utrecht, Netherlands; email: R.C.H.Vermeulen@uu.nl

[5]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, 3584 Utrecht, Netherlands

[6]MRC/PHE Centre for Environmental Health, Department of Epidemiology and Public Health, Imperial College London, W2 1PG London, United Kingdom; email: m.chadeau@imperial.ac.uk

[7]Current affiliation: Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University Medical Center, New York, NY 10032, USA; email: gm2815@cumc.columbia.edu

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Abstract

Derived from the term exposure, the exposome is an omic-scale characterization of the nongenetic drivers of health and disease. With the genome, it defines the phenome of an individual. The measurement of complex environmental factors that exert pressure on our health has not kept pace with genomics and historically has not provided a similar level of resolution. Emerging technologies make it possible to obtain detailed information on drugs, toxicants, pollutants, nutrients, and physical and psychological stressors on an omic scale. These forces can also be assessed at systems and

network levels, providing a framework for advances in pharmacology and toxicology. The exposome paradigm can improve the analysis of drug interactions and detection of adverse effects of drugs and toxicants and provide data on biological responses to exposures. The comprehensive model can provide data at the individual level for precision medicine, group level for clinical trials, and population level for public health.

INTRODUCTION

"The dose makes the poison," first coined by the sixteenth-century Swiss physician and chemist Paracelsus, remains one of the basic principles of toxicology. This maxim states that the toxicity of a chemical is dependent on its concentration in a biological system, implying that all chemicals may be toxic if present at high enough levels. Toxicology and pharmacology practices embrace this concept in traditional toxicity testing, which generally investigates the acute effects of a single chemical exposure in animal models and in vitro systems.

However, the health effects of a chemical depend on numerous factors beyond dose. Christopher Wild (1, 2) addressed this issue in 2005 by proposing the concept of the exposome, a paradigm involving the study of the health effects of cumulative environmental exposures and concomitant biological responses from conception until death (3, 4). The exposome represents a shift toward comprehensive exposure assessment: (*a*) assessing multiple, co-occurring exposures that may be found at low concentrations, similar to real-life exposure conditions; (*b*) understanding how the interactions of exposures with endogenous processes influence their biological effects; and (*c*) identifying critical windows of exposure over the life course. By taking into account the complexities of chemical exposures and organisms' unique biochemical makeups that impact metabolism, the exposome concept will enable a more nuanced understanding of the environmental influences on human health (5).

Here, we broadly review the exposome and its applications in biomedical research. We posit that the adoption of the exposome concept in pharmacology and toxicology will enable substantial advancements in the understanding of chemical toxicities and drug responses. Exposome-based approaches may improve identification of low-frequency exposures as well as detection of widespread exposures with small effect sizes on health outcomes. We provide a vision for the future of exposome research and suggest guidelines for the implementation of the exposome concept in pharmacology and toxicology.

COMPONENTS OF THE EXPOSOME

Exposures

The exposome is composed of the entire set of environmental exposures throughout the life course. This definition encompasses exposures of all types, ranging from individual-level exposures that arise from exo- and endogenous processes (e.g., smoking, radiation, diet, physical activity, infectious agents, psychosocial stress) to general exposures that impact populations (e.g., climate, air quality, urban environment, social capital) (1–3). Exposures can be monitored externally (i.e., measured outside the body) or detected in biosamples for information on an individual's internal dose.

Biological Responses

The original definition of the exposome was refined by Wild (2) and Miller & Jones (3) to include the concept of biological responses. Biological responses represent physiological alterations that are induced as the result of environmental exposures, such as metabolic changes, protein modifications, DNA mutations and adducts, epigenetic alterations, and perturbations of the microbiome (3). Investigating biological responses to exposures provides a better understanding of toxicity mechanisms as well as the interindividual variability in susceptibility to toxic insults. Biological responses can also provide information on transient exposures that cannot be directly measured.

AN ENVIRONMENTAL COMPLEMENT TO THE GENOME

Variance in health outcomes, or phenotypes (*P*), result from contributions from genetic (*G*) and environmental (*E*) factors (i.e., $G + E = P$). In this paradigm, *G* is represented by the genome, while the exposome, which captures *E*, can be conceptualized as the environmental analog to *G*. While greater attention has been placed on the characterization of the genome, recent evidence suggests that the contributions of environmental factors may be equally, or more, influential in determining human health outcomes. For example, a large meta-analysis of 2,748 twin studies found that the contribution of the environment across thousands of complex human phenotypes was nearly equal to that of genetics (6), and a study in monozygotic twins found that the average risk attributable to genetics for 28 chronic diseases was just 19% (range, 3–49%) (7).

Rapid progress in genomics has resulted from the highly organized nature of the field of genetics and from large-scale initiatives, such as the Human Genome Project (8), that have spurred discoveries and the development of low-cost, high-throughput sequencing technologies. However, characterizing the exposome is a far more challenging task. Environmental exposures are dynamic, varying widely in detection and concentration throughout the life course. Capturing the breadth of exposures that comprise the exposome requires the integration of data from numerous sources and platforms. Until recently, progress in understanding *E* has been hindered by a lack of low-cost, high-throughput technologies for exposome profiling, but recent advancements in analytical tools and approaches show promise to enable rapid advancements in the field, as discussed below.

TOOLS TO MONITOR EXOGENOUS EXPOSURES

Measurement of exposures in our surroundings can provide information about the sources and routes of exposure, address temporal variability of exposure, and provide estimates of historical exposures (9, 10). Researchers have employed several methods to quantify exogenous exposures, ranging from the population (measurements, modeling, geographic information systems, remote sensing) to the individual (questionnaires, measurements) level. Recent technological developments have enabled more comprehensive measurements of environmental factors for population-level (e.g., moving from large-spatial scale assessments to hyperlocal maps) and individual-level [e.g., ecological momentary assessments, sensors, accelerometry, and global positioning system (GPS) tracking] assessments.

Exogenous Exposure Assessment at the Population Level

The assessment of exogenous exposures at the population level can provide local-scale exposure estimates over broad geographical areas, enabling large epidemiological investigations that link

exposures with health outcomes. Generally, population-level exposure assessment relies on the integration of sensor technologies with mathematical modeling approaches.

Remote sensing. Remote sensing is the science of obtaining information about objects or areas from a distance, typically from aircraft or satellites. Remote sensing techniques can identify exposures related to the urban environment, such as air pollution, temperature, and green space (10). For example, van Donkelaar et al. (11) estimated global fine particulate ($PM_{2.5}$) concentrations by combining information from three satellites in conjunction with a chemical transport model and ground-based sun photometer observations. The $PM_{2.5}$ estimates, predicted at a spatial scale of 1 km × 1 km, corresponded well to available ground-based data ($R^2 = 0.81$) (11). New technologies, such as the TROPOspheric Monitoring Instrument, provide more spatially and temporally resolved data on air quality in addition to data on specific atmospheric constituents (e.g., formaldehyde, methane, nitrogen dioxide). Satellites can also estimate the normalized difference vegetation index, an indicator of green space (12)—which can be integrated with Google Street View images for a comprehensive assessment of the quality, accessibility, and esthetics of the urban environment (13)—and outdoor light-at-night exposure (14, 15). While remote sensing data are increasingly becoming available at higher temporal and spatial resolutions, these measures do not necessarily translate to exposure at the individual level, necessitating validation and integration with individual-level information (see the section titled Exogenous Exposure Assessment at the Individual Level).

Mobile and stationary sensing. External exposure information is often sampled at a limited number of locations, generally as part of a national measurement network or through study-specific measurement campaigns. Both approaches have limitations: National networks (e.g., air pollution) have limited geographical coverage (i.e., in the 60% of the US urban areas with regulatory monitoring, there are on average only two to five monitors per million people and 1,000 km^2) (16), while study-specific measurements are usually conducted over a short period (17). To provide dense spatial information over a long period, one solution is to use distributed sensor networks, which consist of low-cost sensors deployed in large numbers in urban environments. Examples of such projects are the 100 × 100 West Oakland Community Air Quality Study, wherein a dense network of 100 black carbon sensors has been deployed for 100 days, and the AERIAS project (Eindhoven, The Netherlands), in which a network of 35 air quality sensor boxes has been deployed since 2013. Although the application of such networks is still limited due to the limited validity of low-cost sensors (18), technological advances to improve the validity and pricing will result in dense information on air quality, noise, and temperature in urban environments. Mobile monitoring platforms, which can be equipped with high-grade measurement equipment to cover a large geographical area, have also been proposed for this purpose (16, 19). Mobile measurement campaigns have been small, but several recent efforts have started to implement sensors in professionally driven fleet vehicles, including trams in Karlsruhe, Germany, and Zurich, Switzerland, and Google Street View cars in Oakland (16, 20, 21). The latter effort resulted in unprecedented citywide concentration maps of annual daytime nitrogen monoxide, nitrogen dioxide, and black carbon at a 30-m spatial scale.

Modeling. The availability of satellite measurement and geospatial information allows for increasingly accurate estimations of population-level exposures. However, such data are often incomplete in time and space and collected at different geospatial resolutions. As such, modeling approaches are necessary to concatenate information and to distill stable, long-term spatial patterns from time-resolved data. Empirical and geostatistical models, including land use regression,

kriging, and maximum entropy models, have been considered and will need further elaboration, especially as data resolution in time and space increases.

Exogenous Exposure Assessment at the Individual Level

Although population-based estimates are invaluable for epidemiological purposes, individual-level information is more actionable, can be used for personalized advice, and provides possibilities to relate individual external exposure information to internal dose and associated biological responses. Personal sensors have become more mainstream, for example, in measuring physical activity (e.g., Fitbit, Jawbone, etc.). In addition, the ubiquitous presence of smartphones provides new opportunities for individual measurements of exogenous exposures.

External sensors. A wide range of novel sensor technologies is emerging. Personal location data can easily be obtained through GPS devices, enabling the integration of exposure maps with location tracking for individualized exposure estimates (22). Triaxial accelerometers calculate physical activity (steps and metabolic equivalents); several research-grade activity devices are available (e.g., Actigraph; Intelligent Device for Estimating Energy Expenditure and Activity), but there has been a recent boom in commercial activity trackers, such as Fitbit, Jawbone, Apple Watch, and Polar, which have varying degrees of concordance with research-grade trackers (23). Nieuwenhuijsen et al. (24) reviewed the advances in personal sensing technology for external assessment of a broad range of environmental exposures, including air pollution, temperature, and green space. While some devices show promise, the reliability and specificity of low-cost sensors remains a limitation (18, 23).

Besides active sensors, passive individual dosimeters can also be used for exposure monitoring. For example, the use of silicone wristbands, which passively sample individual exposures to organic compounds, can be a useful monitoring technique in large studies and in remote populations (25, 26). After collection, wristbands are analyzed with high-resolution mass spectrometry for a wide range of chemical compounds, including polycyclic aromatic hydrocarbons (PAHs), pesticides, phthalates, and industrial compounds. Recent field evaluations found that these wristbands provide valuable (semiquantitative) information on a variety of chemical compounds, with reasonable correlations between many chemical (e.g., organophosphate flame retardants) concentrations in the wristband and in matched urine samples (27–29).

Smartphone-based sensors and assessments. Due to the high penetration rate of smartphones (approximately 80% of the US and 65% of the worldwide population), data collection of external measures via smartphones has become possible. Smartphones can integrate internal sensors, including accelerometers, GPS, barometers, thermometers, and ambient light sensors (30, 31); contain functionality, such as a camera and microphone, to record personal exposures, such as occupational and environmental noise (32); and enable communication-based research tasks, such as administrating electronic questionnaires and relaying information from other sensors. Context-sensitive ecological momentary assessments, which integrate sensor information with information collected through short questionnaires on the smartphone, provide new opportunities for integrating information on external exposures with data on well-being and health (33).

Personal sensors. An increasing number of personal sensors are being developed to monitor heart rate, blood glucose, blood pressure, muscle activity, temperature, and sweat production (34). Similar to environmental sensors, many are still under development and will require validation

before implementation in large-scale patient and general population studies. However, maturation of sensor technology for physiological and contextual data will open up new research possibilities, especially for integration with external exposure sensor data.

The Future of Exogenous Exposure Monitoring

Over the last decade, several major technological advances have produced increasingly time- and spatially resolved information on exogenous exposures. While many of the technologies are at an early technological readiness level (TRL), some are approaching Levels 4 and 5, which indicates that these technologies have been validated (TRL4) and demonstrated (TLR5) in relevant environments (35). Thus, we expect that many of these technologies will be widely applied in population studies in the near future, allowing improved exposure assessment and linkage to both internal dose and associated biological responses.

ASSESSING INTERNAL DOSES AND BIOLOGICAL RESPONSES

A critical component of the exposome is linking exogenous exposures to both internal dose (pharmacokinetics or toxicokinetics) and the associated biological response (pharmacodynamics or toxicodynamics). Exposure to environmental chemicals can initiate local and global changes in gene transcription, enzyme activity, metabolite pathway alterations, and protein synthesis/folding. As a result, micro- and macroscale interactions occur among these systems that can be characterized to study dose–response relationships. Measurements can provide information on acute biological responses that occur at a biologically relevant dose and also on whether long-term alterations in physiology—that is, markers of exposure memory—have been detected from environmental stressors occurring years or decades before (36–38).

Since high-dimensional analytical platforms now provide omic-level characterization, application of the exposome framework has the potential to provide deeper insight into how environment influences human health. The following sections describe the use of omic approaches to better understand the role of exposures in human health, with a specific focus on measuring biological response. Overall coordination of metabolism and homeostatic control occurs through different regulatory mechanisms and signaling pathways; dysregulation due to exposure can be measured by alterations through connected hubs in a biological network (39). Thus, we close with a discussion of the role of multi-omic approaches in the exposome framework.

Metabolomics

The metabolome includes all low molecular weight (<2,000 Da) chemicals present in a living system and represents a functional output of genetic disposition, environment, diet, and health, and it was recently estimated that the collective spectrum of chemicals in the human metabolome may include 1 million or more compounds (40). Current approaches, which are based on untargeted analyses using high-resolution mass spectrometry with advanced data extraction and annotation algorithms, allow measurement of more than 20,000 chemical signals in biological samples, spanning endogenous metabolites, dietary chemicals, microbiome-derived metabolites, environmental chemicals, commercial products, and drugs (41–43). Because endo- and exogenous chemicals are simultaneously detected, metabolomics provides an integrated measurement to link exposure to internal dose, biological response, and disease pathobiology (44–46). By not limiting detected analytes to those selected a priori, untargeted metabolomics greatly expands surveillance of environmental chemicals, detection of new xenobiotic metabolites, and identification of previously

uncharacterized pollutants (47–51). Curation of metabolomics data to provide confirmed identification of the chemicals associated with the mass spectral features represents a critical research need. Despite this limitation, the unbiased and global characterization of metabolic responses enables the generation of new hypotheses for delineating toxicological mechanisms underlying chemical exposures in model systems (52–58) and humans (59–70). These advantages combined with its relatively high throughput and low cost have poised metabolomics to be a key analytical platform for the exposome.

Transcriptomics

Gene expression is the process whereby the genetic code is transcribed to RNA, which is used to initiate and direct protein synthesis. Regulation occurs through a complex series of interactions that controls the amount of RNA and protein produced. Thus, gene expression changes due to the exposome can reflect underlying changes that lead to functional alterations in the proteome and metabolome, providing a direct link between exposure and phenotype. Chemical exposures have been linked to distinct gene expression profiles in humans and in model systems (71). Transcriptomic analyses of exposure to environmental chemicals have primarily used DNA microarray hybridization, which utilizes 40,000–50,000 molecular probes (72–76). Next-generation sequencing (e.g., RNA-Seq), which has recently become widely available, allows measurement of messenger RNAs, microRNAs, small interfering RNAs, and long noncoding RNAs, providing new insight into gene expression changes associated with chemical exposures (77–80). The availability of databases, such as the Comparative Toxicogenomics Database, that contain curated information on chemical, gene, phenotype, and disease relationships (81) greatly enhances the biological interpretation of transcriptomics within the exposome framework. The biological information from these databases provides a basis to compare mechanisms identified in model systems and changes observed in human populations, which can be used to define chemical-specific profiles.

Proteomics

The measurement of proteins to assess signaling, inflammation, oxidative stress, and tissue damage is well established in clinical settings, epidemiology, toxicology, and pharmacology. While gene expression provides insight into mechanisms underlying protein synthesis, the measure of protein levels and post-translational modifications provides a more direct measure of functional changes. Targeted measurement of a limited number of proteins is typically completed using enzyme-linked immunosorbent assays, but new multiplexed, bead-based assays can measure more than 50 proteins using a small amount of biological material (82, 83). In humans, proteomic studies have identified immune- and inflammation-related proteins associated with exposure to diesel exhaust (84, 85) and PAHs (86). Continued development of multiplexed proteomics has considerable potential for characterizing biological responses. Untargeted proteomics via high-resolution mass spectrometry has expanded the understanding of protein and gene function (87), though traditional untargeted proteomics is challenging due to the difficulties of detecting low-abundance proteins in serum. Protein adductomics has emerged as a key technology for assessing chemical exposure to reactive electrophiles, reactive oxygen species, and lipid peroxidation products (88). Current adductomic platforms enable the measurement of more than 100 human serum albumin adducts at the nucleophilic locus Cys34, which have been used to assess exposure to lifestyle factors, indoor stove smoke, and ambient air pollution (89–91).

Epigenomics

Gene expression is modified through epigenetic changes that alter the genome without changing the underlying DNA sequence. These changes, which occur through DNA methylation (or related processes) or histone modifications, result in long-term changes to gene expression that can persist during cell division and be inherited by subsequent generations. Stressors, including chemical exposures, injury, disease, and infection, can lead to distinct epigenetic signatures that remain long after the initial event (92); epigenomics is a key approach to evaluate exposure history and allostatic load (36, 93). In human cells, methylation of DNA occurs at the CpG dinucleotides in the cytosine C5 position. While tens of millions of CpG sites are present within the human genome, current high-throughput assays based on massively parallel sequencing of DNA with bisulfite conversions provide measures of up to 850,000 CpG sites. Epigenome-wide association studies have found distinct methylation patterns associated with chemical exposures, providing insight into mechanisms underlying biological responses and disease (94–100). While epigenomics studies have largely focused on single or easy-to-characterize exposures, application within the exposome framework will provide insight into the interactions between the genome and proteome and characterize long-term and generational changes due to environmental exposures.

Multi-Omic Assessment of the Exposome

The availability of omic-level data to assess biological responses allows new opportunities to understand environmental influences on human health. By integrating response measures from metabolomics, proteomics, transcriptomics, and epigenomics, it is possible to develop a systems biology–level understanding of how exposures influence critical biochemical processes. Aggregated biological response patterns, which combine toxicology and pharmacology with molecular and environmental epidemiology, represent a new paradigm to delineate mechanisms underlying chemical toxicology (**Figure 1**). In a study of occupational exposure to the volatile organic chemical trichloroethylene (TCE), integration of untargeted metabolomics with established biomarkers of immune function and renal damage identified unknown metabolites of TCE associated with biological response, which was not found using traditional urinary TCE biomarkers (101). This demonstrates how a limited number of biological response markers can provide insight into the biological changes from chemical exposures. Continued development of statistical approaches to identify interactions among biological response networks (102, 103) and the application of multi-omic approaches to characterize human exposures in cohort studies (104, 105) will spur discoveries in the coming years.

HANDLING EXPOSOME-SCALE DATA

From a practical point of view, exposome data can be classified into two categories: exogenous data compiling heterogeneous measurements of stressors occurring outside the body, including environmental exposures, behavioral and socio-economic factors, and high-throughput molecular (omics) data essential to the characterization of internal doses and biological responses. As such, exposome data are diverse in nature, and the strength and complexity of the correlation structures across the variables are different (106, 107). Most omics data—and to a lesser extent, exogenous exposure data—share a high-dimensional nature in which the number of variables is large and can exceed the number of observations n. Several approaches have been proposed to accommodate this situation and have been reviewed previously (108–110).

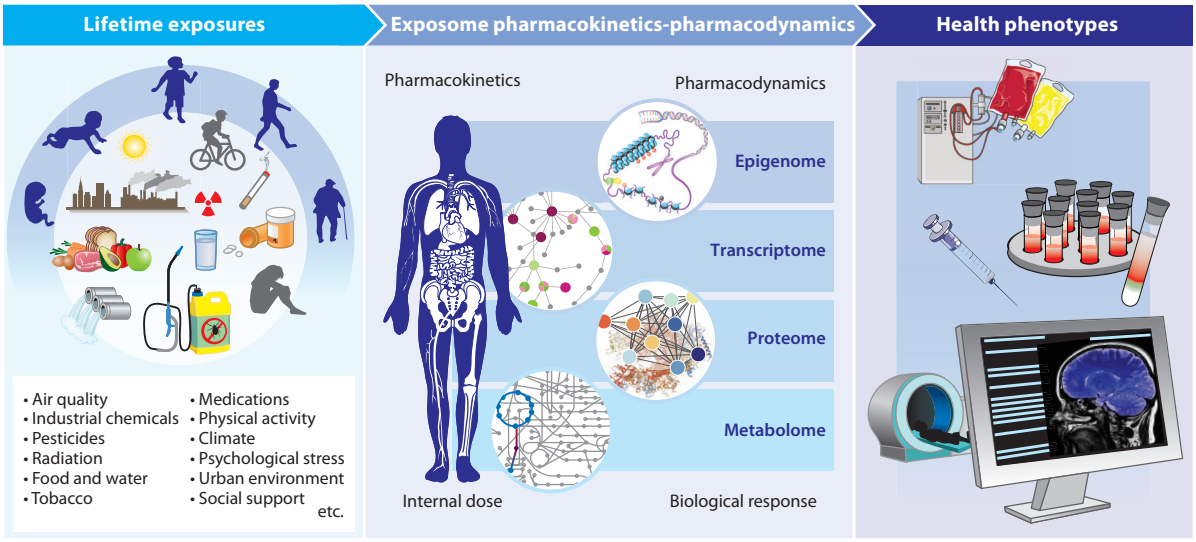

Figure 1

The exposome as an analytical framework linking exposures to outcomes. The exposome attempts to measure, integrate, and interpret the complex exposures faced throughout the life course. Further, the exposome measures how these complex exposures impact our biological systems and provides a connection to health and disease outcomes. Head MRI image adapted from Pixabay (**https://pixabay.com/en/head-magnetic-resonance-imaging-mrt-254866/**), CC0.

Univariate Methods

Univariate approaches separately assess the association between each variable in the predictor matrix (exposures or omics data) and the outcome of interest, which are coupled with multiple testing-correction strategies via controlling the family-wise error rate or the false discovery rate. Due to the correlation across predictors, the same information is, at least partially, tested several times across the *p*-tests actually performed. To avoid overly conservative corrections that hamper statistical power, it is warranted to define the effective number of tests performed across the actual *p*-tests, for example, through eigen decomposition (111) or resampling (106, 112, 113) techniques.

Dimensionality Reduction

Owing to the complex effects of exposures, there is a need to jointly model omics or exposome data in relation to the outcome. Dimensionality reduction techniques build on the correlation within the data to summarize lower dimensions at the cost of a minimal loss of information. The resulting latent variables (components) can be constructed in an unsupervised manner [e.g., through principal component analysis (PCA)] to identify the fewest components that minimally distort the original dataset. Plugging these components into regression models evaluates how the main drivers of the variation in the original data are related to the outcome. Supervised alternatives [e.g., partial least square models (PLS) (114)] directly construct latent variables, capturing the maximal variation in the predictors relevant to the outcome.

Variable Selection

Variable selection approaches identify a sparse subset of predictors most relevant to the outcome. Variable selection is achieved in a regression framework through the use of a penalty imposing

a constraint on the estimates of the regression coefficients. The least absolute shrinkage and selection operator (LASSO) (115) and elastic net (116) perform variable selection by shrinking the regression coefficients of the least influential variables to zero. The penalization principle can also provide shrunken loadings coefficients in PCA [sparse PCA (117)] and PLS [sparse PLS (118)]. Bayesian methods for variable selection, which generally rely on the estimation of the posterior distribution of a binary p-dimensional vector defining the model space, have also been proposed. Several algorithms have been developed to search in the vast (2^p dimensional) model space to scale to full-resolution omics data (119–122).

Mixtures

Combinations of exposures may have different, and possibly stronger, effects than the effect of each exposure separately. This warrants modeling the effect of exposure mixtures, notably by considering interactions among exposures (123–125). However, these approaches rely on strong assumptions in the number, order, and parametric form of these interactions. Such assumptions are challenging for exposome data, wherein some effective exposures are not measurable or are unknown. A two-stage strategy has recently been proposed to explore exposure mixtures to (*a*) identify exposures of interest and (*b*) fully investigate their potential interactions (124, 126). However, this approach assumes that exposures active in a mixture could be detected based on their marginal effects. To better capture the complexity of the exposure mix, including potential (unmodeled) interactions, and better account for multivariate/pleiotropic effects, models accommodating multivariate exposures and responses, such as PLS, have been proposed (127).

Functional Characterization

Exploring the biological effects of the exposome depends on the functional characterization of identified exposome-related molecular alterations. Because the regulation of cellular metabolism involves multiple types of molecules interacting in complex cascades, data from exposome profiling should be complemented with an investigation of the biological pathways affected by the identified molecular signals. Ontology-based tools interrogating existing databases are rich sources of information to identify biological pathways corresponding to candidate biomarkers. These tools are established for gene expression data (128–130) and full-resolution mass spectrometry profiles (131). For omics platforms lacking ontology tools, biological interpretation can be informed by linking these platforms to other omics data whose functional role is better characterized. Integrative analyses can be performed with univariate models that assess pairwise associations across biomarkers from different platforms (132).

Data Integration

To capture the complexity of multi-omic correlations, it is necessary to explore long-distance relationships using dimensionality reduction techniques and variable selection approaches. Sparsity is essential to ensure results interpretation but may not be sufficient to ensure a detailed understanding of the complex patterns exhibited by omics data integration. The incorporation of prior knowledge on functionally relevant structures can improve the interpretability of results and be used as a grouping factor in sparse statistical models. Resulting (sparse) group LASSO (133) and (sparse) group PLS (134) select the most relevant set of (predefined) groups and can identify the most influential markers within each group.

Networks

Omics profiling and integration approaches produce prioritized lists of (multi-)omic markers that jointly reflect the molecular effects of the exposome. Exploring their interconnections via network topologies provides insight into their modes of action. Network modeling relies on pairwise correlations and the selection of influential edges (e.g., significance assessment via permutations or stability analyses). When sparsity is imposed on the network topology, modules may emerge that identify sets of multi-omic markers that are functionally close, facilitating their functional interpretation. Supervised alternatives, as defined by differential networks (135–137), will account for differences in subpopulations by linking two nodes if their relationships differ across two populations (e.g., cases and controls).

Longitudinal Analyses

Longitudinal data are key for identifying causal relationships and enable explicit modeling of the processes linking exposures and biological responses. For repeated exposome or omics measurements, analyzing trajectories through classification methods [e.g., sequence analyses (138), time warping algorithms] assesses autocorrelation across observations to identify time-resolved patterns characteristic of life stages of higher susceptibility to exposure and/or disease. Dynamic approaches, including multistate models, which are defined by a set of ordered states (compartments) reflecting the evolution of the individual state, and estimated transition probabilities, ensure the best reconstruction of the individual trajectories (139). Integrating biomarkers in these models may help identify the step(s) of the pathological pathways on which they exert effects, further elucidating their functional roles.

Computing Solutions for Exposome Data

The analysis and integration of complex, high-dimensional exposome data represent a considerable computational burden. These challenges call for optimized implementations and the development of publicly accessible databases, which could be efficiently handled by cloud-based computing. Many methods, such as univariate approaches, can be parallelized and would directly benefit from shared computing. Computational optimization of multivariate approaches and network inference can be achieved by parallelizing calibration procedures and/or stability analyses.

INCORPORATING THE EXPOSOME IN PHARMACOLOGY AND TOXICOLOGY

The broad purview of the exposome captures many of the molecular- and systems-based pathways and networks generally included in the analysis of the effects of drugs and toxicants.

The comprehensive chemical profiling inherent within the exposome paradigm could improve the assessment of adverse drug interactions. With thousands of drugs now detectable in single mass spectrometry–based assays, it will be possible to test the internal dose of multiple compounds and their metabolites. This platform has been adopted in drug testing programs for athletics (140), and the same approach could be used to test for possible dangerous interactions among pharmaceuticals, recreational drugs, dietary factors, supplements, and other chemical exposures in clinical populations. This approach could be especially helpful for conditions that require drug cocktails or in patients with multiple conditions whose combined treatment results in an unplanned drug cocktail. An exposome-level analysis not only provides the concentrations of the potential

exposures/drugs but also provides complementary information on key biological pathways and networks altered by the administered compounds.

Interindividual variability is recognized and appreciated among the pharmacology and toxicology community. The field of pharmacogenomics has helped tailor treatments to individuals with particular enzymatic profiles that influence drug metabolism. The exposome could provide more precision to this approach by providing information on dietary and lifestyle factors that impact drug responsiveness. The field has long recognized that many dietary factors induce cytochrome p450 enzymes, and an exposome approach could help capture the network state of an individual's metabolism. An omic-level assessment of metabolites via metabolomics could help identify adverse biological effects prior to the onset of symptoms. For example, when treating a patient with asthma, information on an individual's exposures to a wide range of potential triggers (e.g., pet dander, particulate matter, other allergens) would be extremely beneficial for determining a personalized treatment plan. This is precisely the type of comprehensive approach the exposome provides.

While mechanistic studies have historically taken a reductionist approach to determine precise modes of action, the field of pharmacogenetics must embrace the fact that humans are rarely exposed to single chemicals. Humans are subjected to chemical mixtures and the exposome provides a means to measure these exposures and assess their biological impacts. However, assessing the effects of complex mixtures presents numerous challenges, especially in the regulatory toxicology arena, which plays an important role in the drug and product approval process. The field has moved away from the analysis of single targets toward the analyses of adverse outcomes at a pathway level. Namely, the adverse outcome pathway (AOP) framework recognizes that many chemicals converge on similar biological pathways, thus assessing risk by examining disrupted pathways may be more informative than looking at single targets (141, 142). As the AOP framework advances, it is clear that targeted pathways are, in reality, networks that mirror findings from omic-scale biology. Thus, the exposome is entirely consistent with the move toward studying adverse events at pathway and network levels.

FROM PRECISION MEDICINE TO POPULATION-BASED PUBLIC HEALTH

Traditionally, clinical practice has focused on treating disease phenotypes. However, the development of platforms for comprehensive patient characterization as well as computational tools for identifying patterns linked to disease show promise for personalized medicine, wherein prevention and treatment strategies are based on an individual's unique characteristics (143). To date, precision medicine approaches have focused on genomics to identify variants associated with disease risk and pharmacogenomics for determining responders/nonresponders to treatment strategies. Currently, there are genetic tests for over 2,000 clinical conditions, and this number is expected to increase as genetic testing becomes cheaper and more readily available (144).

In the United States, over 85,000 chemicals are registered with the EPA for manufacture, import, and use in commercial products. Additionally, approximately 40,000 pesticide formulations, 100,000 dietary phytochemicals, and 5,000 other chemicals are approved for use as inert ingredients and 7,500 compounds are registered by the US Food and Drug Administration as drugs or food additives. An individual's history of these exposures over a lifetime—that is, their chemical experience—may contribute directly to phenotype and health. In almost all cases, limited information is available about these chemicals in terms of their distributions across populations, the health effects of low-level exposures, and the influence of complex mixtures encountered in real-world scenarios. The adequate characterization of an individual's chemical burden will require the

ability to measure upwards of 1 million chemicals routinely across the lifespan in a cost-effective and efficient manner (40). This need crystallizes a grand challenge for analytical chemistry, clinical science, precision medicine, epidemiology, toxicology, and exposure science.

Approaches for measuring individual exposures include varying levels of uncertainty. For example, studies have employed heuristic models calibrated to chemical biomonitoring surveys to prioritize toxicity screening (145); geospatial models calibrated using mobile, stationary, and remote-sensing techniques to predict respiratory exposures (146, 147); recall surveys to estimate dietary exposures and their links to disease (148); ambient exposure measurements to provide estimates of exposure to large groups; and breathing zone samplers to estimate exposure over short- and long-term periods (149, 150). In all cases, these approaches provide generalized estimates and do not assess internal exposure or biological relevance. Targeted biomonitoring assesses exposure biomarkers in biological samples to estimate body burden of previously identified chemicals. While biomonitoring has proven invaluable, chemical coverage is limited. For example, the National Health and Nutritional Examination Survey applies targeted biomonitoring approaches to measure 212 chemicals in a cross-section of the US population, which represents only 0.02% of the 1 million chemicals that may comprise the human exposome. Thus, the ability to assess exposures on this magnitude far exceeds the capability of targeted platforms, and advanced chemical profiling techniques are required.

High-resolution metabolomics (HRM), which uses gas or liquid chromatography with ultrahigh-accuracy mass spectrometry, is the most promising analytical technology for an exposome platform for precision medicine (41, 45, 55, 151–153). Due to increases in scan speed and data extraction algorithms, modern instruments are capable of detecting 20,000–100,000 unique chemical signals in small volumes (<150 μL). Including triplicate injections improves reliability of peak detection when studying exposures that occur in a small subset of the population. Combined with a technique known as reference standardization, HRM can determine absolute concentrations of biomarkers for the assessment of potential risks from exposures (153).

Additionally, HRM is cost-effective relative to other biomonitoring platforms (45). Further cost reduction is possible through focused analysis of high-abundance metabolites and exposure markers. HRM reliably detects approximately 1,000 common, endogenous metabolites, commercial products, and drug metabolites with coefficient of variation (CV) less than 10% (41, 151, 153–155). By limiting detection to chemical signals with low CVs, reducing runtimes, and employing automation, samples could theoretically be processed with a throughput of 500 samples/day (125,000 samples/instrument-year) at a cost of $5 per sample. In addition, minimally invasive sampling systems could simplify biosample collection (156; P. Samant, M.M. Niedzwiecki, N. Raviele, V. Tran, D.I. Walker, et al., submitted manuscript). Thus, sufficient chemical coverage for the purposes of precision medicine and the detection of environmental exposures and related bioeffects could be obtained at a low cost with available technology. The cost and throughput of exposome profiling by HRM could enable regular internal exposure assessment, possibly through a direct-to-consumer product and/or as part of an annual health checkup. This information will not only provide important insight into the role of environment in human health but also a critical public health tool for environmental chemical surveillance and hazard identification, linking precision medicine to improved population health.

CONCLUSIONS

The exposome paradigm embraces cutting-edge technologies that strive to capture every chemical entity to which we are exposed, moving far beyond a targeted list of compounds measured by traditional methods. Although molecular interactions are already critical in pharmacology and

toxicology, systems biology and networks play increasingly important roles in both fields. The exposome paradigm can help provide systems-level analysis to better understand interactions such as drug–drug, drug–supplement, drug–dietary factors, and drug–chemical exposures or combinatorial interactions thereof. Further, the exposome provides concepts and tools that complement traditional approaches in pharmacology and toxicology and should lead to a better understanding of the complex environmental factors that influence the response to drugs and toxicants.

DISCLOSURE STATEMENT

G.W.M. receives royalties for his book *The Exposome: A Primer* (4).

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Errata

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