HHS Public Access

Author manuscript

Curr Epidemiol Rep. Author manuscript; available in PMC 2020 April 26.

Published in final edited form as:

Curr Epidemiol Rep. 2019 ; 6: 93–103.

The metabolome: A key measure for exposome research in epidemiology

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Abstract

Purpose of review—Application of omics to study human health has created a new era of opportunities for epidemiology research. However, approaches to characterize exogenous health triggers have largely not leveraged advances in analytical platforms and big data. In this review, we highlight the exposome, which is defined as the cumulative measure of exposure and biological responses across a lifetime as a cornerstone for new epidemiology approaches to study complex and preventable human diseases.

Recent findings—While no universal approach exists to measure the entirety of the exposome, use of high-resolution mass spectrometry methods provide distinct advantages over traditional biomonitoring and have provided key advances necessary for exposome research. Application to different study designs and recommendations for combining exposome data with novel data analytic frameworks to study complex interactions of multiple stressors are also discussed.

Summary—Even though challenges still need to be addressed, advances in methods to characterize the exposome provide exciting new opportunities for epidemiology to support fundamental discoveries to improve public health.

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Compliance with Ethical Standards Conflict of Interest

Douglas I. Walker, Damaskini Valvi, Nathaniel Rothman, Qing Lan and Dean P. Jones each declare no potential conflicts of interest. Gary W. Miller serves as Editor in Chief of the journal Toxicological Sciences and does receive renumeration for this, but it does not present a conflict.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Exposome; Metabolome-wide association study; Precision medicine; High-resolution metabolomics; Environmental epidemiology; High-resolution exposomics

1. Introduction

Precision medicine provides a new paradigm for healthcare, where focus is shifted from treating a single disease phenotype to prevention and treatment strategies based on an individual's unique characteristics [1, 2]. Currently, there are genetic tests for over 2,000 clinical conditions, and many more genetic markers are likely to be incorporated into emerging risk stratification models. However, disease etiology is multifactorial and driven by a combination of genetic, environment, nutritional and lifestyle factors, which represent key measures to evaluate disease risk [2, 3]. Thus, there is a clear need to improve assessment methods for exposures and to apply a broad approach in evaluating these exposures in order to fully incorporate the concept of the exposome into precision medicine.

2. The human exposome

To emphasize the importance of applying state-of-the-art and comprehensive approaches to evaluate the environment in studies of disease etiology, Christopher Wild introduced the concept of the exposome in 2005, which he defined as a framework for measuring environmental stressors that "encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards [4]." The exposome is envisioned as a complement to the genome, where an individual's history of exposure and how these exposures interact with the genome defines risk for disease.

Unlike the genome, which remains stable over time, the exposome varies on timescales ranging from seconds to decades. As a result, exposures that occur episodically and/or that have relatively short biologic half-lives can be especially challenging to assess. A key approach to help address this is to conduct longitudinal studies that collect biological samples at multiple times in the life course. Further, in addition to directly measuring the actual exposure or its metabolites, metabolomics has the potential to measure patterns of exposure-specific biologic perturbations, including those that could persist even after the exposure ceases. For example, Miller and Jones defined the exposome as [5]: "The cumulative measure of environmental influences and associated biological responses throughout the lifespan, including exposures from environment, diet, behavior, and endogenous processes." Within this framework, exposures include external stressors, processes internal to the body, socioeconomic influences and psychological factors [6]. By characterizing the exposome in terms of a cumulative measure of environment and biological response, this definition suggests that at least for some risk factors multiple measures of an individual's exposure over the entire life course might not need to be measured, and that instead small molecules related to the exposure effect and maladaptation could be a surrogate for that exposure.

To date, no unified method exists to characterize the sum involvement of environment in disease etiology. Two main strategies are emerging from recent exposome research projects, one using personal sensors with geospatial monitoring and another using biological samples with broad measurement of biomarkers representing exposure, biological response and adverse effects [7, 8]. Both are enabled by computational power of big data and provide exciting new opportunities for implementing the exposome into environmental health and precision medicine research [9, 10].

3. Implementation of the exposome

One of the critical requirements for translating the exposome from concept to practice is the development of methods that allow measurement of exposures on the scale consistent with the chemical burden experienced by an individual over a lifetime. In the United States, close to 81,000 chemicals are registered with the Environmental Protection Agency (EPA) for manufacture, import, and use in commercial products, including 68,000 registered under the Toxic Substances Control Act and 13,000 chemicals declared exempt, while approximately 40,000 pesticide formulations, 100,000 phytochemicals, and 5,000 inert ingredients have been approved for use [11]. The majority of these are registered as the parent compound, and do not include abiotic and biotic transformation products that could occur during manufacture, commercial use, storage and environmental transport, or due to host biological processes. Current estimates suggest the potential for upwards of a million chemical exposures experienced over a lifetime [9, 12]. Common exposure assessment approaches are not capable of characterizing exposure on this scale.

A challenge for exposure science to address the exposome at this scale lies in the level of uncertainty which is acceptable for exposure assessment. Methods that provide exposure estimates for large populations, such as remote sensing or based upon geographical location, are limited by accuracy at the individual level. In contrast, targeted biomonitoring, which uses specific and sensitive methods to measure known biomarkers of exogenous chemicals, provides a direct estimate of internal dose [13]; however, the capability to expand biomonitoring beyond a few hundred chemicals to thousands or tens of thousands is cost- and resource-prohibitive, often resulting in underpowered studies that can only detect strong effects [14]. Recent advances in analytical chemistry approaches are beginning to provide the scale of biomonitoring needed to implement exposome research. The human metabolome, which contains all low-molecular weight (<2,000 dalton) chemicals present in a biological sample, has been identified as a key measure of the exposome. The metabolome includes all endogenous biological metabolites, the chemicals from human-environment interaction, and reactants arising from interaction of these compounds with enzymatic and bacterial processes [15]. Proteins, DNA, polymers and other large molecules are not considered components of the metabolome because they require different approaches for measurement; none-the-less, certain chemical modifications of these macromolecules can be detected as breakdown products [16, 17].

The metabolome, which includes chemicals from core nutrient metabolism, lipids, the microbiome, diet-derived chemicals, phytochemicals, pharmaceuticals, commercial products and environmental contaminants, can help integrate the environment and genetics, and can

be directly studied for its impact on disease risk. Enzymes for the core pathways associated with basal metabolism are encoded within the genome and conserved across humans with metabolites present at tightly regulated physiological ranges. Characterizing the endogenous metabolites from these pathways is a functional measure of the genome, which is influenced in multiple ways by epigenetic and transcriptional mechanisms and also by distribution and post-translational modifications of proteins. Exogenous chemicals absorbed by a host, include compounds present in diet, drugs, microbiome, commercial products and environmental chemicals are detectable within the metabolome, either as the compound initially exposed to, or transformation products. These xenobiotics represent the exposome contribution to phenotype.

Xenobiotics influence biological processes through local and global changes within an organism, resulting in micro- and macroscale interactions between environmental chemicals and endogenous processes encoded by the genome. In some cases, toxicant-target interaction results in enhanced clearance of environmental chemicals and in other cases in the formation of reactive species that are more toxic than the original exposure. Genetic polymorphisms influence xenobiotic clearance and bioactivation, resulting in differences in metabolism and response from environmental exposures across a human population [18]. Metabolomics can be useful to characterize such interactions. Thus, the human metabolome can be used to assess the presence of an exposure and also to provide a framework for study of exposure-response relationships (Figure 1).

4. Recent advances in methods for measuring the human metabolome

Methods for characterizing the human metabolome were initially focused on development for precision medicine, disease biomarker discovery and nutrition [19, 20]. Application demonstrated these approaches not only provided measurement of endogenous metabolites, but were sensitive enough to detect exogenous chemicals and the metabolome was responsive to factors outside of the host, such as differences in diet or geographical location [21–23]. In these studies, untargeted approaches were found to be useful by not limiting measures to *a priori* selected analytical targets.

Targeted methods are developed to measure specific, known analytes in a population to test pre-defined hypotheses. As such, critical issues for sample collection and processing, chemical identification, quantification relative to authentic standards, and reproducibility, are addressed prior to analyses. Costs escalate in association with the number of targeted chemicals that are analyzed. Untargeted analysis uses methods that maximize the number of chemicals that can be measured in single sample and categorize their importance for identification using a metabolome-wide association study (MWAS) framework, which systematically evaluates association of each detected chemical with an outcome or disease. These analyses are analogous to GWAS, except the metabolic profile, rather than genetic variants, are tested as disease risk factors. As a result, untargeted metabolomics can be used to detect uncharacterized, unexpected and previously unknown exposures and metabolic products linked to disease. Because of the reliance on untargeted methods, analytical platforms that provide quantitative measures and the ability to identify molecules are required [24, 25].

While initial efforts in untargeted metabolomics were focused on using NMR, limited sensitivity to low-level compounds does not make these instruments useful for exposome applications [26]. In contrast, ultra-high-resolution mass spectrometers (UHRMS) and adaptive algorithms for processing complex mass spectral data now makes possible detection of over 100,000 chemical signals in blood, including environmental chemicals present at levels 100–1000 times lower than endogenous metabolites [27, 25, 9, 28]. The key advantage of available mass spectrometry methods is derived from the high mass resolution (>60,000) and mass accuracy, enabling separation of *m/z* differing by <2.5 parts-per-million. UHRMS profiling of blood plasma samples obtained from healthy individuals has indicated measure of metabolites from more than 80% of the pathways present in the KEGG database and detection of a broad spectrum of environmental chemicals [29]. Because of the high-mass accuracy and resolution, very low intensity peaks can be differentiated from background noise with high-sensitivity [27, 30–33]. For low abundance signals, analyses with multiple technical replicates improves confidence in detection as well as quantitative reliability [34].

An important limitation for current untargeted metabolomics methods is that analytical standards are not available for most detected chemicals and concentrations are reported as ion intensities. To make such data quantifiable in the future, an analytical strategy called reference standardization was developed using pooled samples analyzed within each batch [35, 27]. Known concentrations within the reference sample can then be used to determine a chemical response factor and calculate analytical sample concentrations based on single-point calibration. The benefits of this approach are that targeted quantification is only required in the reference sample, chemicals do not need to be selected *a priori* and population-wide estimates of chemical concentrations can be determined without having to re-analyze samples with chemical standards. By supporting quantification of large numbers of chemicals detected in human samples, reference standardization can provide the systematic biological and environmental chemical measurements required for risk assessment and harmonization across multiple laboratories.

The number and types of chemicals detected in biological samples is greatly expanded by combining complementary strategies for mass spectrometry. These include using alternate chromatography approaches, which are used to separate compounds before detection, and different types of mass spectrometers [23, 36–39]. Analysis by liquid chromatography (LC-UHRMS) and gas-chromatography (GC-UHRMS) provides the most comprehensive complementary platforms for metabolome- and exposome-wide association studies [40]. LC-UHRMS metabolomics platforms are best suited for measurement of polar molecules with specific functional groups, or large, non-polar molecules that contain these functional groups (such as lipids, fatty acids and sterols), making it useful for measures of endogenous metabolites, drug and environmental chemical metabolites. Many environmental chemicals, including volatile organic chemicals, brominated flame retardants, organohalogens, pesticides, hydrocarbons, perfumes and solvents are volatile enough to be introduced into the gas phase when heated and do not contain the functional groups that are required for detection on the LC-UHRMS. Thus, GC-UHRMS provides the best sensitivity and selectivity for these compounds. The combination of these platforms enables measure of both exposure and biological response, providing an integrated framework that can be used

to link environmental exposures to internal dose, biological response and the metabolic changes of disease.

Identification of mass spectral signals is one of the key challenges in untargeted chemical profiling. Many detected ions do not match metabolites listed in metabolomic or environmental chemical databases, and authentic standards are not available. Current efforts focused on leveraging computational approaches that assign annotation confidence have provided improved prediction of metabolites present in chemical databases [41–43]. For annotating unknown spectral peaks, numerous tools can be used for characterizing ion fragmentation patterns to predict possible identities and biotransformation products of parent metabolites [44–47]. Continued efforts focused on developing new chemical databases that house both environmental chemicals and endogenous metabolites as “MS-Ready” structures and development of new computational approaches is expected to rapidly improve annotation capabilities of untargeted mass spectrometry data in exposome research [48–50].

5. Exposure-response relationships in untargeted metabolomics analyses

Data structure and the relationships among features detected in untargeted metabolomic experiments allow a systems-biology approach to understanding molecular mechanisms [51, 52]. While single feature-outcome relationships can assist in identifying biomarkers of disease risk or exposures, they often do not adequately describe variability across a population spectrum and, as a result, suffer from reproducibility among populations and effectiveness as diagnostic or prognostic tools. Internal data structure, which can be represented using network-based topology approaches, has been used to characterize unknown features through relationship to known biological pathways, compare metabolism across species and assess systemic responses to environmental exposures and disease [35, 53–55, 36]. Combined with alternative omic data, such as methylation, gene expression, cell sub-populations or proteomics, a functional approach can be used to identify data-driven relationships across multiple phenotypic data sets, including exposure, and represents a key area of research for the exposome [51, 56, 10].

Conceptually, interconnecting pathways and networks are equivalent; the structure can be described by a set of edges connecting nodes that represent metabolites and enzymes. Thus, pathways can be mapped on top of correlation structure and metabolite subsets tested for pathway enrichment, which evaluates if more metabolites from a given pathway are present than would be expected by chance. An initial limitation of this approach is the need to assign metabolite identities prior to performing the enrichment tests, which is complicated by uncertainty in annotation of mass spectral data. This has been overcome by development of the pathway enrichment tool *Mummichog,* which was developed specifically for use with untargeted high-resolution mass spectrometry data and incorporates complexity of untargeted mass spectral data while isolating biological effects and reducing Type I error [57]. The algorithm has been applied to a range of studies examining metabolic effects of disease, drug and environmental exposures [36, 58, 59].

To date, this pathway enrichment approach has been used to identify alterations in endogenous metabolism. Studies of polycyclic aromatic hydrocarbon metabolites in US

Armed Services Personnel showed that expected metabolites of environmental chemicals are detected and quantitatively related [60]. Thus, the feasibility is established to develop an identical approach for xenobiotic metabolite biomonitoring. With development of powerful new tools that predict *in silico* biotransformation and high-throughput multi-cellular exposome screening assays [61, 62], an exposure enrichment analysis can be used to mathematically evaluate greater exposures in one population relative to another. This has the potential to overcome many of the limitations of single biomarker approaches in epidemiology and improve reliability of environmental risks of disease identified in population studies.

Demonstration of how metabolomics can be applied using the framework described in Figure 1 to provide important insights into the underlying mechanism of exposure-disease relationships is demonstrated by a recent study of occupational exposure to the degreasing solvent, trichloroethylene (TCE) [63]. In this study, untargeted metabolomic profiling was used to evaluate early biological effect, of TCE exposure by comparing metabolic differences between 80 healthy workers using TCE and 95 unexposed, matched controls [63]. Full-shift TCE levels were evaluated for all workers, and blood samples were collected following completion of the work shift [64]. Using a MWAS, all detected mass spectral signals were tested for association with exposure. Metabolites associated with exposure included known TCE detoxification products, unidentifiable chlorinated compounds and endogenous metabolites. To elucidate biological response, pathway enrichment analysis was completed, and identified disruption to purine catabolism, decreases in sulfur amino acid and bile acid biosynthesis pathways; which are consistent with known toxic effects of TCE. Metabolites associated with exposure were also tested for their relationship with urinary TCE exposure biomarkers and physiologic endpoints, supporting known or suspected disease associations, including immune and renal effects. Thus, external exposure was linked to internal dose and biological response, providing insight into molecular mechanisms of exposure-related disease etiology. Most notably, TCE metabolites associated with physiologic endpoints included compounds that had not been previously described, identifying potential new mode-of-actions for TCE toxicity that would not have been detected if only targeted analyses were completed.

6. Metabolomic applications in epidemiology studies of disease

Due to the ability to characterize a diverse series of endogenous and exogenous metabolites in biological samples, metabolomic approaches have rapidly gained acceptance as an important tool in population health research. Results demonstrate application to measure the metabolome using small volumes of blood, urine, stool, saliva, exhaled breath condensate, cerebral spinal fluid, biopsies and other hard and soft tissues has the potential to inform on possible mechanisms underlying disease [65–70]. Furthermore, current analytical strategies are high-throughput and available at a relatively low cost, making possible analysis of large studies on the order of 1,000 to 10,000 samples [11, 60, 71, 72]. Thus, metabolomic methods are poised to provide a key analytical platform for exposome research in epidemiology.

A fundamental aspect of the exposome is to assess the occurrence and impacts of environmental exposures across the lifespan. The use of life course epidemiology approaches, which aim to elucidate biological and environmental processes that operate across an individual's life course and how exposure at different periods influence disease risk [73], is of critical importance for exposome research. However, most existing evidence is currently from case-control or cross-sectional studies that do not allow establishing a clear temporal relationship between exposure, intermediate effect biomarkers and disease. Recently, metabolomics characterization of amniotic fluid, cord blood, and maternal/child urine or serum samples have been used to assess complex fetal-maternal exposures, and have potential to be linked to developmental problems [59, 74–77]. Newborn dried blood spots have also been proposed as a promising specimen for metabolomic profiling and have been used to identify metabolic biomarkers of future risk of cancer and other childhood diseases [78]. The integration of untargeted metabolomics in large-scale prospective pregnancy and childhood cohorts with continued follow-up of participants towards adulthood is a key requirement for the characterization of the exposome over the lifespan. As exogenous exposures and endogenous metabolites are time-varying, future study designs can be benefited by the integration of metabolomics at multiple time points; such approaches are currently lacking.

The use of occupational studies to understand the effect of workplace exposures on health can further provide key insight into disease risk factors and early biological effects of exposure. Metabolomic approaches have been applied to a range of occupational exposure studies [79, 80]. As indicated above, metabolomic associations with occupational TCE exposure demonstrates the power of using untargeted approaches to characterize the effects of chemical exposures [63]. Additional metabolomic studies of occupational exposures include welding fume exposures, metals, shiftwork, military deployments, farming, automotive exhaust and pesticide plant workers [81–86].

Untargeted metabolomic profiling of tissues, urine and blood in population studies can detect environmental chemical metabolites and previously uncharacterized biomarkers in human populations [87, 76, 31, 32, 27, 23]. Using MWAS, metabolic alterations can be associated with exposure levels and used to evaluate exposure-dependent relationships in biological pathways. To date, multiple exposures have been assessed, including air pollution, persistent organic pollutants, proximity to industrial operations, metals, perfluorinated substances and plasticizers [36, 88–95]. As with all observational studies it is important to control for confounding, which can be accomplished by study design ensuring comparability of "exposed" and "unexposed" subjects and by using questionnaire-based data and biological markers of known or suspected confounders. Replication of biologic response findings in other studies is critical to rule out false-positive associations. Further, where feasible, study designs that evaluate populations before and after an exposure takes place (e.g., before and after a large seasonal variation in an environmental exposure, or where appropriate, controlled low-level exposure studies) can be very useful to help established a causal relationship, as well as exposure intervention studies that evaluate subjects during the exposure and post-intervention when exposures are reduced. Finally, following up observed associations in experimental *in vitro* and animal studies can also help to support causal relationships in humans.

The application of metabolomics to the study of disease risk, screening, and treatment efficacy has generated some promising initial findings, although the field is still in its infancy. These include studies of neurodegenerative diseases [96], type II diabetes [97], cancer [98], human immunodeficiency virus (HIV) infection [53], tuberculosis [99], malaria [100] and cardiovascular disease [71, 72]. A critical next step in the application of metabolomics to the study of disease etiology and early disease detection will be the use of longitudinal studies, which have already shown their utility [101, 102, 72], and especially when repeat biological samples are collected and stored over many years. These studies will allow the direct measurement of exposure to exogenous and endogenous compounds at multiple points during the life course, which is especially important for environmental exposures that have relatively short half-lives and/or do not bioaccumulate, and the assessment of the trajectory of metabolic changes from those exposures leading to disease.

The use of untargeted metabolomic methods provides a systematic measure for conducting a metabolome- and exposome wide association study of disease. To understand the complexity of the human exposome, new data analytic strategies need to be adopted in epidemiology studies. Identifying relationships between environmental factors and disease, and establishing causality, will require strategies that incorporate multiple-levels of measurements that capture exposures, biological response and disease [103–105]. To avoid complication by factors related to reverse causality and identify exposures from the environment contributing to development of disease, so called “meet-in-the-middle” approaches hold promise for untargeted methods applied to human studies [8, 106]. When performing this type of data analysis, causal relationship between disease and environment is evaluated through a prospective search for intermediate biomarkers related to past exposure and associated with disease development. If overlapping associations are identified, it reinforces a potential causal interpretation of the exposure-disease association. As an additional step, the proportion of the association explained by intermediate biomarkers can be quantified using causal mediation analytical methods [107]. The associations identified using this framework can also be evaluated through animal exposure and disease models, which help establish biological plausibility. Target populations to support this approach are not limited to life-course studies, and existing studies of children or adults with previously collected biologic samples and questionnaire data can be used within this framework. For example, exposure can be tied to disease using other exposure assessment methods, such as geospatial data, exposure questionnaires, and remote sensing; exposure can be linked to intermediate biomarkers in existing occupational exposure studies that may reduce confounding due to additional exposures; and intermediate biomarkers can be linked to disease using already established or new prospective cohorts. Untargeted metabolomics can be integrated with each type of data to facilitate overall linkage of exposure to outcome.

7. Conclusions

Incorporation of the exposome into epidemiology research will improve the ability to understand the effect of environmental exposures on human health. In many cases, disease arises from a complex series of environmental, lifestyle and genetic factors that are not possible to elucidate using single biomarker approaches. While still rapidly developing,

technology now exists to provide the functional measures of environment and biological response that potentially allows comprehension of the complex, human chemical experience, and efforts are underway to evaluate harmonization of these methods across laboratories [108–110]. Platforms based upon UHRMS now allow measurement of 10,000–100,000 chemical signals using minimal sample volumes and are cost-effective. While current technologies allow analysis of 40 samples per day (12,500 samplers per instrument-year) at a cost of approximately $100, with appropriate investments in development of automation, chromatography and bioinformatics, analysis of up to 500 samples-per-day (125,000 samples per instrument-year) and cost as low as $5 per sample may be possible. As a result, barriers to incorporate metabolomic approaches for measuring the exposome have been lowered and deserve consideration as a cornerstone in epidemiological biomarker studies. This technology, combined with complementary advancements in genetics, transcriptomics, epigenetics, proteomics, imaging and bioinformatic approaches for identifying patterns in this complex data provide exciting new opportunities for fundamental discoveries in human health.

Acknowledgements

This work was supported by funds received from the National Institute of Environmental Health Sciences (ES026561, ES023515, ES029328, ES019776, ES028903 and ES030163), the National Institute of Mental Health (MH107205), National Institutes of Health Office of the Director (OD018006) and intramural funds received from the National Cancer Institute. Funding sources did not direct the study.

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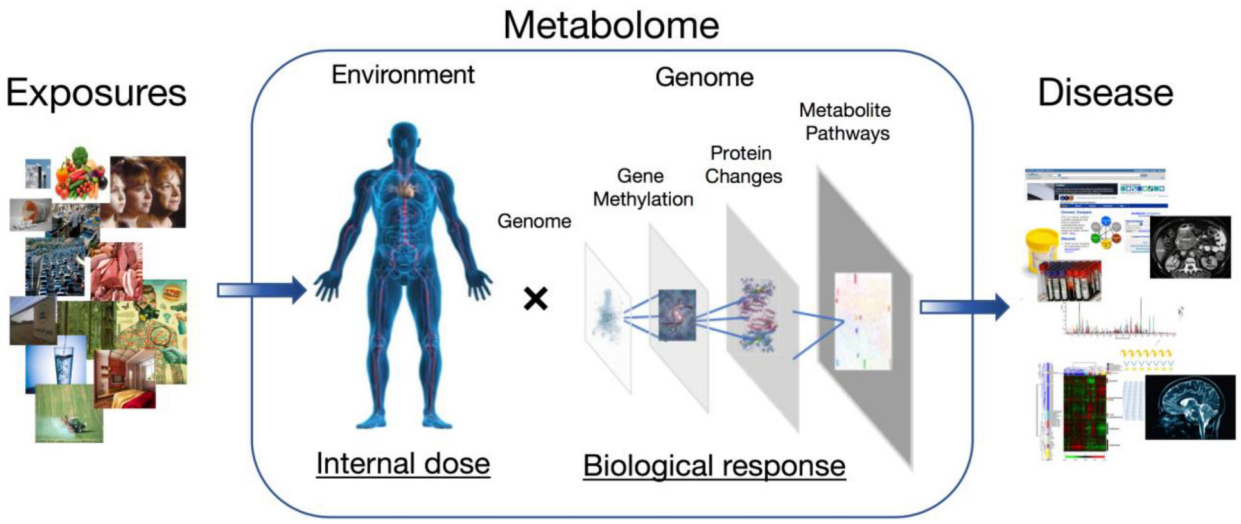

Figure 1:

Framework for the metabolome as a central measure for linking exposure to internal dose, biological response and disease. Environmental chemicals absorbed by a host, which are detected within the metabolome in either the parent form or as transformation products represent a measure of exposure internal dose and the exposome contribution to metabolic phenotype. These compounds can influence biological processes through local and global changes within an organism, resulting in micro- and macroscale interactions between environmental chemicals and endogenous processes encoded by the genome, the functional measures of these interactions can be detected as alterations to metabolic processes. By detecting metabolites from most metabolic pathways, metabolomic techniques allow evaluation of these biological changes, which represent markers of effective dose and response. Long-term shifts in metabolic processes accompany disease pathobiology and often represent distinct metabolic phenotypes from controls. Thus, the human metabolome can be used to assess the presence of an exposure and also to provide a framework for study of exposure-response and disease relationships. (**Reprinted from Elsevier Books, Douglas I. Walker, Young-Mi Go, Ken Liu, Kurt D. Pennell, Dean P. Jones; Metabolic Phenotyping in Personalized and Public Healthcare, Pages 167–211; Jan 1, 2016; with permission from Elsevier) [111].**