authors found 2,796 unique formulae of the chemical exposome, including the insect repellent diethyltoluamide (DEET), the pesticide omethoate, and the carcinogen diethylene glycol (DEG), which were present in every sample. The airborne biological diversity observed in this study was enormous with over 2,500 species identified, 5.11M single-nucleotide polymorphism (SNPs) in 108 pan-domain species across all samples. This number is comparable to the number of SNPs evaluated in the human gut microbiome (101 bacterial species; 3.98M SNPs at the individual level, 10.3M for all samples) (Schloissnig et al., 2013).

Based on the same analytical advances described above in relation to metabolomics in biological samples, the external exposome also benefits from untargeted LC-MS technologies. They allow the chemical compounds present in air, water, and surfaces in human habitats and the workplace to be profiled in an exposome-wide manner (McCall et al., 2019). They have even been proposed as a tool for use in forensic science (Kapono et al., 2018).

2.3. Biological responses: incorporating omics into exposome research

Early biomarkers of effect, that is, before clinical symptoms appear, are needed to identify early environmental exposures in humans, in particular during sensitive windows of exposure, such as pregnancy:

> Biomarkers of effect are measurable molecular, cellular, biochemical, physiologic, behavioural, structural or other alterations in an organism occurring along the temporal and mechanistic pathways connecting exposure to chemicals and an established or possible health impairment or disease. (National Research Council, 2006)

Ideally, effect biomarkers reflect subclinical changes before the onset of disease. Consequently, they range from early biological changes (e.g. enzyme induction responses) to altered structure and function. Effect biomarkers can help in identifying early effects at low doses, establish dose–response relationships, explore mechanisms, and increase the biological plausibility of epidemiological associations. In addition, they can improve the risk assessment of specific chemical families as well as exposure to chemical cocktails.

The use of omics platforms, once reserved for improving clinical diagnosis, patient stratification, and personalised medicine, is becoming increasingly common in the detection of subtle biological changes in the non-diseased general population (Everson & Marsit, 2018; Maitre et al., 2023). This is partly due to the feasibility of their application in large populations ($N > 1000$) in epidemiological

settings, and thanks to their high throughput at reduced costs. Until recently, omics efforts have focused mainly on the identification of altered genes at the genome-wide level (genomics), allowing geneticists to move beyond the analysis of single candidate genes and to perform whole DNA sequence screening. However, while the genome represents the inherited set of DNA instructions needed for the creation and functioning of an organism, it is the environment that shapes and channels the biological potential of an individual during its normal or pathological development. Therefore, more recently other omes have come to the fore leading to the emergence of new omics techniques that facilitate the study of the interplay and intermediate steps between the biological blueprint and an individual's physiological responses and interactions with the environment (Peters et al., 2021). These include epigenomics, the identification of the epigenetic markers of gene expression acting without alteration of the genetic sequence and considered the "cell memory"; transcriptomics, the study of the expression levels of protein-coding messenger RNA (mRNA) and non-coding microRNA (miRNA); and proteomics, the field concerned with the production, behaviour, and interactions between proteins.

Among more recently developed omics are those that complement the other methods by enabling studies of the internalisation of exogenous exposures and immediate physiological response. These include metabolomics aimed at identifying, quantifying, and performing profiling of metabolites (as described in section 3.1 above) as well as metagenomics which allows the characterisation and quantification of all the genomes of the gut microbiota (microorganisms, including bacteria, archaea, fungi, and viruses, that live in the digestive tracts).

The abundance of existing omics techniques allows the events leading to pathological development or the adverse health outcomes at the early stages of the affected process to be pinpointed. For instance, different omics have proved useful in detecting early biological perturbations before the appearance of clinical symptoms in longitudinal epidemiological settings (Maitre et al., 2022), predicting later cardio-vascular and metabolic diseases or neurodegeneration (Liu et al., 2019; Westerlund et al., 2021; Wingo et al., 2022). These platforms have also been used in vivo and in vitro toxicological studies of endocrine disrupting chemicals to improve understanding of these mechanisms.

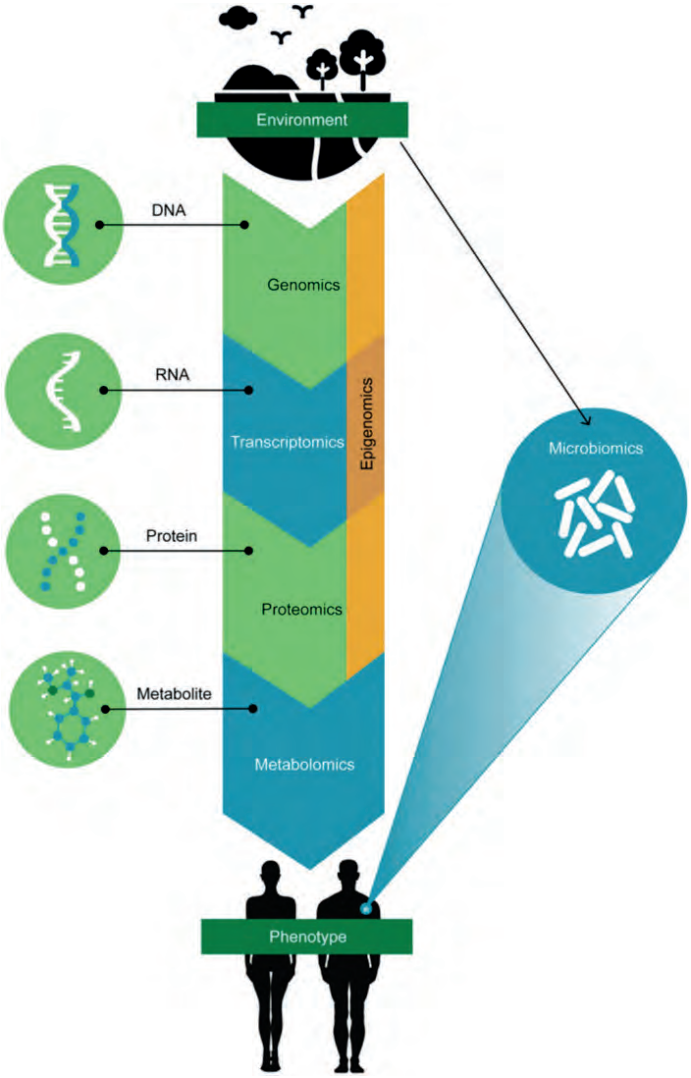

FIGURE 6. Overview of -omics technologies used to profile biological responses to the environment, leading to phenotype changes. Commensal microorganisms residing within (gut and other organs) and on (skin) the human body, collectively known as the *microbiome*, are largely influenced by host-microbe interactions that are reflected in the microbiome compositional and functional profiles.

SOURCE: Yu et al. (2022), An evaluation of the National Institutes of Health grants portfolio: Identifying opportunities and challenges for multi-omics research that leverage metabolomics data, *Metabolomics*, *18*, 29 (30 April), https://doi.org/10.1007/s11306-022-01878-8, under Creative Commons Licence Attribution 4.0 International, https://creativecommons.org/licenses/by/4.0/.