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Rediscovering the Ethical Priority of the Most Actionable System of Biomolecules - the Metabolome

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Preface

A remarkable feature of US federal investments in human genetics has been the availability of parallel funding for studies examining ethical, legal and social implications (ELSI). This funding has allowed ELSI researchers to develop new strategies to understand genetics, evaluate the benefits of genetic testing, and propose health policy that maximize the promise while minimizing harms [1]. Despite successes, a consequence of this investment is the preoccupation with what is arguably the least actionable system of biomolecules, human DNA. In contrast, the most actionable system of biomolecules, the metabolome, is grossly understudied, despite its often more alarming ELSI.

Support for ELSI research grew directly out of the National Institutes of Health (NIH) Human Genome Project, and continues to be overseen as an extramural research program in the National Human Genome Research Institute (NHGRI). Over the past three decades, this funding mechanism has become the largest source of extramural funding for bioethics research in the world. Not surprisingly, the majority of ELSI research proposals focus on genome research and clinical applications of genetic testing. Unfortunately, this emphasis is out of step with the multi-omics revolution in the life sciences that has followed in the wake of the human genome project. Armed with new insights and tools from genomics, a wide array of biological fields are studying synergistic connections among biological pathways and phenomena—and importantly, focusing their efforts on the system of biomolecules that are much more amenable to intervention.

The metabolome, the totality of small molecules in a biological system [2], is arguably the most impactful biological sub-system for health and wellness [3]. While DNA forms a foundation for biology, the action of molecular biology is happening above the genome. Whether referring to

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the molecular interactions occurring endogenously (from the genome and among the cells and organs) or exogenously (from behavioral and environmental chemical exposures), the metabolome is the highly dynamic molecular system that serves at the nexus (Figure 1). The metabolome is the molecular system most proximal to phenotype (the observable characteristics of an organism) and, as such, is key to mechanistic studies of health and disease.

Metabolomics initially focused on cellular metabolic pathways. Driven by technological advances, a broader definition is gaining acceptance, emphasizing all “omics”-scale research on small molecules (<1,500 Da) [2]. Metabolomics research, compared to other ‘omics sciences, encompasses a broad range of structurally diverse molecules, from microbiome secondary metabolites and food-derived molecules to xenobiotics [2]. Metabolomics can be considered an umbrella discipline encompassing a wide range of sub-fields, including lipidomics, exposomics, fluxomics, etc.

Metabolomics is exciting because it brings knowledge of mechanisms to health. Translation of metabolomics knowledge into treatments may be more straightforward because most drugs are themselves metabolites, small molecule agonists or antagonists of signaling cascades and metabolism [4]. Given the key role of small molecules at the intersection of biological and environmental systems (Figure 1), metabolomics has unique potential in a personalized medicine framework and provide the biomolecularly realized impact of social determinates of health. Metabolomics builds off of a

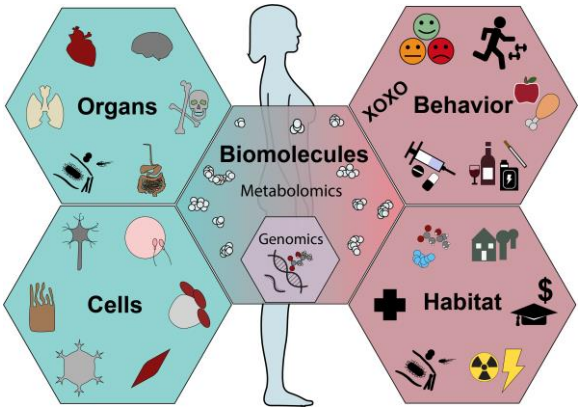

Figure 1, the metabolome serves as the nexus of the interacting systems that shape health

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100+ year legacy of characterizing biochemical pathways, products, and reaction intermediates (classic metabolites), laying the foundation of vast majority of biotechnological advances, including nearly all current pharmaceuticals, pesticides, and vital nutrients [5]. With new tools, immense chemical libraries, and integration with other forms of big data, metabolomics has entered a golden era of discovery, and well deserves the central place in federal funding initiatives, institutes and research programs.

The Genome's Place

The 100+ year legacy of metabolites demonstrates that metabolomics is poised to have a greater claim to success in medicine than genomics. Yet, this is not to undervalue the genome, only to put the genome in a more reasonable place in biology and health. The genome transcends the health of the individual, and reflects a history and a future of our species. It has been well said that "nothing in biology makes sense except in light of evolution" [6] and the genome is that fundamental molecule of the evolutionary process. Moreover, genomic variation has demonstrated a level of predictive power for many diseases and health risks; although, it is equally fair to say that the predictive power of the genome alone has questionable utility for complex diseases [7].

Most aspects of health and disease are complex, not directly attributable to genes. Even considering emerging excitement and concerns with CRISPR [8] and other gene editing technologies, these gene-based approaches will, forever, be subsidiary to the vast array of metabolite-based interventions that impact our life. One common misconception of genomics is that the combination of the genome, transcriptome and proteome determines function, phenotype, and health; however, with respect to much of biomolecular activity, the system of gene expression remains subordinate to the substrates, products and other modifiers involved in metabolic activity [9]. Thus, even with perfect data on gene expression, this information still

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only conveys what might happen during a metabolic process, in contrast, information from the metabolome uncovers what is actually happening [10].

Unlike genomics, research into the ELSI of metabolomics is essentially non-existent[11]. In two broad areas, metabolomics has less ethical concerns: on average, 1) metabolomic data is less ancestry-informative; 2) metabolites are a more dynamic system than genes and gene products; our current metabolome profile is less fixed than our germline profile, creating opportunity for intervention. Some ethical issues in genomics have analogues in metabolomics and can serve as foundations, but differences are nevertheless substantial, so these genomic foundations are unlikely to provide direct solutions to metabolomics ELSI.

Privacy

The potential loss of personal privacy from the metabolome is greater than most realize. The metabolome is shaped by where you live and what you do, and consequently bears information on your environment and your practices; drugs, diet, and various environmental exposures are traceable in the metabolome. Aspects of your behavior, your practices, your biology, are not only impacting the metabolome in your body, but the metabolites you leave behind. The metabolome can be characterized in your kitchen, bedroom, your keyboard at home or work [12-14]. Indeed, metabolites left on phones can be used to build a behavioral profile of the phones' owner, and even to match them back to together [13]. The metabolome is therefore a molecular fingerprint different from DNA, but equally impactful, and more so if the objective is to understand human actions rather than human ancestry.

Health and the built environment are deeply tied [15]. Metabolomics is poised to make significant contributions to this area of research [16], but not without some major concerns for privacy, misinterpretation, and misuse of results. Visualizations of the molecules of the built environment

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not only reveal an individual's contact with their habitat, and the habitat's impact on the individual, but also the diffusion of a chemical material culture within the habitat, such as sanitizers, medication, personal care products, foods, drinks and their additives [14]. The chemical tracing of behavior, from the individual behaviors to the history of an item, has major implications for a range of sciences, and certainly, for ethics. One of the more profound examples is the presence of cocaine in the built environment. Most banknotes in circulation in the U.S. carry detectable levels of cocaine [17]. As proof of principle, one study applied untargeted metabolomics to reveal behavior in an apartment [14], including associated belongings; unsurprisingly, cocaine was detected although none was used by the occupants. Many metabolites are "sticky" and can be found on objects months later [13]. Detection of such molecules may not reflect a person's current behavior, but rather their actions six months ago or the actions of a previous owner of the object. Preventing mis-interpretation and over-interpretation of such findings will be a major concern that intersects privacy, exposomics, and health; policies to protect privacy and human rights from the over-cavalier use of metabolomics are needed.

Imagine a future where we have readily, publicly available, comprehensive, metabolomic data for everyone, for their environment, and over time, and imagine we have the capacity to deeply analyze such data. We now see biological mechanisms. We now understand those mechanisms and have the chemical tools to impact biology and health in ways the genome alone could never achieve. We can transform healthcare. But in this future, privacy is a fantasy, and the potential misuse of metabolomics data is a major concern. We should be prepared for a world where molecular tools threaten personal privacy in ways that are difficult to appreciate fully today.

Policy

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The United States Genetic Information Nondiscrimination Act (GINA) of 2008 is a federal law that provides some protections to those using genetic tests or family history, to learn about their health risks; health insurers and employers are unable to request, require or use this genetic information to discriminate. The only metabolites specifically covered under this law are those that directly predict genotypes, mutations, or chromosomal changes. Any other metabolites are excluded from these protections. For example, GINA does not cover current health conditions and specifically excludes metabolites that are directly related to a "manifested disease, disorder, or pathological condition that could reasonably be detected". This legal condition is problematic in metabolomics. Genetic mutations in one enzyme often affect the direct product of that enzyme, but through cascade effects almost certainly affect the downstream metabolic products, plus any pathways regulated by downstream products, and the cells' compensatory mechanisms. Moreover, the vast majority of health associated metabolites are uninformative of genetic variation. In other words, at this time, there are no protections for most health and behavior associated metabolites. This is a distinct privacy risk from other non-genetic health information, such as weight and medical use, because the metabolome is all encompassing, not targeted, and there are no guidelines currently for delineating that which is relevant and reasonable for insurers from that which needs further protection from discrimination.

Intellectual property

Metabolomics-based biomarker tests are patentable; as an example, the U.S. company Metabolon holds over 30 U.S. patents on biomarkers and biomarker identification methods, covering diseases such as atherosclerosis, diabetes, amyotrophic lateral sclerosis, cancer, etc., with additional applications to the study of drug mechanism of action, response to drugs, and the link between gene expression and metabolite production [18-22]. Patenting specific metabolites for treatment purposes may be more challenging. For metabolites present in nature and already structurally described, only patents covering method of use or production processes would be

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possible. Nevertheless, chemical modification may be straightforward and lead to derived patentable novel chemical matter [23], which raises questions on who owns a trivially modified, but otherwise ubiquitous, metabolite.

Naïve use of Race

Through metabolomics, racial/ethnic groups could be stereotyped and compartmentalized in ways that speak more about the worldview of the researcher than the elastic bioculture of people. Attempts at identifying race-specific metabolomic biomarkers have begun [24,25], and while these studies are drafted to improve clinical practice for diverse people, the framing of the problem is naïve to genetic and cultural diversity. Without question, genetic ancestry and cultural practices impact biology and health, and co-associate with culturally constructed racial groups, to various degrees. Even so, the use of race or ethnicity as the primary focus of research is rarely warranted [26]. While ethnicity or racial identifications can have utility in study designs, especially with regards to inclusion of diversity and narrowing down the phenomenon impacting biology, culturally constructed racial groups are merely proxies, often poor, for the underlying genomic and cultural/environmental variables that directly impact health. To have precision, the wiser approach is **not** to invent individual tests for races, but individual test for individuals. So much of metabolomics is shaped by practices and the environment that the construction of race-specific assays creates an unreliable rigidity of people.

Disparities

The data available to science shapes the science. Naturally, this advocates for efforts to include diverse groups within science to avoid reinforcing disparities. Yet, the impact of new and emerging sciences are less understood, and may expose participants to unpredicted risks. These risks maybe more challenging to mitigate in socioeconomically vulnerable populations compared to the general public. This is the most universal protection dilemma impacting health

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disparities among underrepresented groups. How do we give people the equal potential for benefit, while mitigating potential risks, especially for the more vulnerable? This is a challenging question for ELSI and metabolomics that intersects and exacerbates all the above concerns of the ethical handling of metabolomic data.

Intersecting race and disparities includes appeals to environmental justice, as build environments in more impoverished areas are likely to provide tangible evidence of disproportionate environmental toxins relative the more affluent areas. Claims based on metabolomics will need careful review, which also includes issues of social justice, privacy, and racial disparities.

Conclusion statement

High impact discoveries, those eureka moments that are paradigm-shifting in science, and life-changing in medicine and health, do not come often. They require deep commitment, sacrifice, often abundant failure and misdirection, which will only be exacerbated if fear of research reduces participation by individuals, groups, and nations. If the 100+ years of history is any indication, metabolites will hold a leadership position in health detection and treatment discoveries for the foreseeable future, and with the advent of metabolomic-scale research, there is hope that the momentum in drug discovery has a new catalyst. The time has arrived to create an ELSI research agenda that recognizes the important role of metabolomics in studies of human health, to enhance the protection of patients who participate in metabolomics research, and develop privacy protections that anticipate the unique challenges that metabolomics analyses will create.

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