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## Sensing metabolomics landscape unfold molecular connectivity between mental illness and drug abuse

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### Abstract

Environmental threats to mental equity have recently gained much attention in the sphere of public and curative health due to their toll on the individual, families, the public, and their economic sphere. Mental health or soundness of mind is important at every stage of life from childhood and adolescence through adulthood to protect the brain from environmental stress. What makes mental health unlike genetic rare disorders is that there is no known single cause for this rising public health issue because it arises from multiple factors. These factors include early adverse life experiences, such as trauma or a history of abuse either because of child abuse, sexual assault or seeing any form of violence, experiences related to other ongoing (chronic) medical conditions, such as cancer or diabetes, biological factors or chemical exposure resulting in hormonal imbalances in the brain, and to a large extent having feelings of loneliness or isolation leading to suicidal action. Furthermore, the increase in mental health and its accompanying conditions depend on environmental with or without behavioral changes due to genetic stability may be associated with drug, alcohol, or substance abuse which is associated with the brain reward circuit which may need to compromise the neural circuit over a wide range of stressors on the human body interacting with the sequential neuronal cell cascade. Although humoral networking is associated with socio-behavioral change, work through family, religious, organizational engagement, and community support play major roles in its solution and management, it is consensually accepted that defining key determinants underlying molecular network altering by epigenetic and genetic factors have promise in empowering future systematic health and personal care including surveillance, prevention, treatment, and monitoring process. In the modern global and urbanization era, emerging new biomedical technological advances such as epigenetic tools, genomics editing, human genomics study utilizing sequencing technology, and reverse genetic resources from worm to animal models have enabled us to take a closer look at mechanisms that could be involved in mental illness and drug abuse or addiction using a pattern of metabolomics and its connectivity reflecting the interplay between mental illness and drug abuse and/or addiction. This paper describes a molecular-driven surveillance platform as a part of the power of prevention to care of populational health which could be beneficial by predicting risk and unfolding the impact of daily lifestyle on human behavior such as food intake, alcohol intoxication, and its outcome likely the effect of metabolism on mental illness and drug abuse. Interaction between environmental cues to neural circuits which may interplay with metabolic networks as well as potential risk resulting in various forms of phenotypic complications and behavioral alteration might be detectable using multi-omics platforms.

**Keywords:** Surveillance tool; Molecular circuit; Polymorphism; Molecular imaging; Mental illness; Drug Abuse; Metabolomics; Interactome

### 1. Introduction

According to the World Health Organization (WHO), mental health is the basis for the well-being and effective functioning of individuals. It goes beyond the absence of a mental disorder; it involves our ability to think, learn, and

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understand one's emotions and the reactions of others. WHO further states that mental health is a state of balance, both within and with the environment [31]. Physical, psychological, social, cultural, spiritual, and other interrelated factors participate in producing this balance. Based on data interpretation by WHO, more than 100 million people suffer from mental health disorders in the Western Pacific Region. Depressive disorders alone are responsible for 5.73% of the disease burden [6]. The Center for Disease Control and Prevention, also asserts that mental health issues are among the most common health conditions in the United States.<sup>3</sup> Also, more than 50% will be diagnosed with a mental illness or disorder at some point in their lifetime 1 in 5 Americans will experience a mental illness in a given year, 1 in 5 children, either currently or at some point during their life, have had a seriously debilitating mental illness and 1 in 25 Americans lives with a serious mental illness, such as schizophrenia, bipolar disorder, or major depression [7].

The WHO goes ahead to define drug or substance abuse as the harmful or hazardous use of psychoactive substances, including alcohol and illicit drugs. One of the key impacts of illicit drug use on society is the negative health consequences experienced by its members [30]. Drug use also puts a heavy financial burden on individuals, families, and society. The evolution of the complex global illicit drug problem is clearly driven by a range of factors. Sociodemographic trends are influential such as the population's gender, age, and the rate of urbanization. Recently Cannabis has emerged as the most widely used illicit substance. The highest prevalence and increase in drug abuse are being reported in West and Central Africa with rates between 5.2% and 13.5% [31]. For example, Amphetamine-type stimulants (ATS) such as "ecstasy" and methamphetamine now rank as Africa's second most widely abused drug type. These are some of the statistics showing why drug abuse is a problem: the harmful use of alcohol results in 3.3 million deaths each year; at least 15.3 million persons have drug use disorders, and there are 148 countries known to be abusing drugs through injection. From these statistics, it is clear that mental health is a serious public health issue that is partly influenced by drug abuse.

Biologically, mental health is widely associated based on hereditary rooted their parental genome, where the stability of inheritance regarding parental genes plays a major role in the similarity and nature of a cell in their decent. There have been ongoing questions as to how the alteration or instability of the genome could come about. Our DNA transmits information contained in the sequential order and combinatorial process of its four nucleotide bases across generations and is the information repository that, in interaction with environmental signals or cues, controls the development of an organism and the cells and organs within it. In cells, the information contained in DNA is translated to proteins via orchestration with other molecules such as exons and introns including structural RNA and messenger RNA. Under the optimal condition after crosstalk between environmental signal and genetic code, messenger RNA is translated to produce proteins, which control the shapes of cells, regulate their chemical reactions and form neurotransmitter receptors and ion channels. With respect to neural development work through neural network or connectivity following the formation of synapses, proteins form guidance cues or control their synthesis; these direct the migration of neurons from stem cells to their correct places in the brain, leading to the establishment of proper connections in the early phase of brain development. To improve preventive power, referring to mental illness and drug abuse from environmental exposure or threat in young adolescence, we proposed to develop a molecular connectivity map from environmental cues to human behavioral alteration using molecular-based risk assessment and prevention aspects as following interactome such as metabolomic driven approach.

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## 2. Impact of Metabolomic landscape and its molecular pattern on Drug Abuse

In previous studies, an emerging body of evidence elicited that metabolomics could influence mental illness and drug abuse [10]. Correlation between stress-mediated mental illness and multigene polymorphism including gene alteration, mutation, chromatin remodeling, and epigenetic modification (e.g., DNA methylation, DNA acetylation, and histone modification) was associated with an interventional barrier in the caring of mental health following a variety of environmental exposure: HIV infection, tuberculosis, substance drug use, food chemicals, and the status of the gut microbiome. [8,23,25,28,29]. For example, molecular alteration interacts with environmental stress-mediated genomic instability reported in several categorized diseases that refer to mental illness, for example, schizophrenia, bipolar disorder, depression, autistic spectrum disorder (ASD). Briefly, Wu et al. (2021) demonstrated that host-microbes could interact with the underlying mechanistic signaling cascade in the case of Amnestic Mild Cognitive Impairment and Alzheimer's disease (AD) [31]. Hu et al. (2014) reported the interplay between gene ALDH2 polymorphism and alcohol intoxication-dependent hypertension [13]. Similarly, an epigenetic study conducted by Liyanage et al. (2017) visualized the connectivity risk related to early exposure of alcohol to genetic vulnerability following epigenetic modification in the study of Fetal Alcohol Spectrum Disorders (FASD) disease integration to represent the interaction between parental and maternal mental health [15]. In addition, the role of the microbiome in depressive disorders was revealed in the study led by Bastiaanssen group in 2020 [3]. Moreover, Earley et al. (2017) illustrated neuronal adaptation augmented by the dopaminergic system in restless legs syndrome (RLS) as a pharmacological model [9]. Regarding the ASD study,

it was suggested that the connectivity between oxidative stress following environmental exposure and alteration of the immune system like dysfunction rely on the pathogenesis [4,20].

In line with previous mental illness and psychiatric reports, Alam et al (2017) indicate that psychiatric disorders resulting from sequential causes rooted in environmental exposure to the human genome go through epigenetic medication, chromatic modification, and inflammation depending on the metabolic status of the gut microbiome niche and their metabolites [2]. The gut microbiome might be affected by mental health wired by neural networks either pro- or anti-oxidative stress modulation in CNS disease exacerbated with neuroinflammation. There are some reports that elicited the connectivity between metabolic modification and mental health and related signaling networks using in vivo experiments. In line with previous findings, a translation study led by Liu et al. (2019) showed that altered glucose metabolism is associated with AD pathogenesis based on evidence such as the metabolic profile alterations of pancreatic tissue and serum results. [13]. The study of targeting molecules in the fasting condition found that mitochondrial protein deacetylase sirtuin 3 (SIRT3) as a molecular stabilizer could interact with antioxidant enzyme SOD2 over metabolic stress in the animal study using APP/PS1 Transgenic mice model of AD. [14].

In a study led by Virmani et al (2007), it was illustrated that drug abuse has been associated with many metabolic disorders such as hyperinsulinemia, hypertension, dyslipidemia, and abdominal obesity and can be caused by early cell imbalances in a variety of important metabolic pathways [26]. It has been shown to be a highly sex-sensitive manner. These initially small metabolic imbalances are thought to cascade over time, leading to greater problems. Some signs that substance abuse can increase the risk of metabolic syndrome include drug addicts being prone to a higher incidence of diabetic complications [19].

Another study conducted by Mitchell et al (2011), further reveals that individuals with serious mental illness (SMI) such as schizophrenia are even more likely to be overweight or obese than other members of the general population [19]. Another study conducted by Correll et al. (2010) confirms that in North America nearly 80% of a sample of over 10,000 people with diagnoses of schizophrenia, bipolar disorder, or depression are overweight or obese, which is a metabolic disorder [7].

Recently, an evaluation report referring to cardiovascular risk indicates that amphetamines generally affect the cardiovascular and nervous systems, exacerbating risk factors for metabolic syndrome [1]. Methamphetamine (meta) addicts suffer from cognitive impairment and abnormal metabolic activity that affect nutritional status. This condition is exacerbated by significantly deteriorating oral health of stimulant abusers, causing improper chewing and thus digestion. Interestingly, a study conducted by Virmani et al. (2007) suggested that undernourishment combined with substance abuse increases the risk of developing metabolic syndrome by increasing cell damage, increasing excitotoxicity, reducing energy production, and reducing the antioxidant capacity of cells [26]. Moreover, a translational study reported that a potential risk factor for developing metabolic syndrome is genetic susceptibility, especially when combined with substance abuse and malnutrition [19].

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### 3. Molecular dynamics can be used as a Surveillance tool

Multi-Omics can be used as a mental health monitoring tool for metabolic complications, as it is a new and sophisticated throughput method that answers most health problems. New evidence shows that various environmental factors include stressors that cause mental illness. Currently, unmet medical outcomes and monitoring platforms in the field of mental illness require the implementation of sensitivity combined with key biomarkers in detection, evaluation, and validation [22]. The use of macromolecular-dependent data analysis-based omics such as bioinformatics in psychiatric disorders and healthcare assessment platforms improves risk gene identification and treatment options by confirming the functional efficacy and recovery status of drugs. There is a possibility. The use of brain function includes behavioral assessment, metabolomics, and neuropharmacological genomics studies [27].

In addition, the interaction of genomics, proteomics, transcriptomics, topomics, metabolomics, and neuroimaging is becoming a powerful tool for analyzing psychiatric disorders, and personalized care for patients known as psychiatric tumors is a very valuable monitoring tool [5]. The use of psychiatric as a monitoring tool has led to several studies, including Allelic heterogeneity loci and studies [5]. In addition, another ongoing study suggests that the gut microbiota and its interactome are also noteworthy for understanding brain damage and developing innovative therapies and diagnostics [16]. Recent detailed characterization of the human microbiome has led to a paradigm shift in human health and disease. Animal models strongly suggest the role of the gut flora in anxiety and trauma-related disorders.

The Microbiota Brain Axis (MGB) is central to this new approach to mental health [17]. Microbiomes play an important role in early life and lifelong stress responsiveness in programming the hypothalamus-pituitary-adrenal (HPA) axis. One

of the major concerns of modern society is to find putative biomarkers that serve as a valuable early diagnostic tool for identifying a subset of patients at high risk of developing neuropsychiatric disorders [17]. The identification of biomarkers in neuropsychiatric disorders has been suggested to provide many important benefits to patient well-being, including prediction of imminent disease, the accuracy of diagnosis, and the level of disease description that guides treatment choices [21].

Presently, the metabolomics approach has opened up new possibilities for the diagnosis of catastrophic illnesses such as neuropsychiatric disorders [22]. Metabolomics-based techniques have the potential to map early biochemical changes in disease and therefore the opportunity to develop predictive biomarkers that can be used as indicators of pathological abnormalities prior to the onset of clinical manifestations of neuropsychiatric disorders [22]. The review conducted by Rhind et al (2020) illustrated various omics strategies for the discovery of biomarkers in neuropsychiatric disorders [21]. It also highlights the early results of metabolomics studies in psychiatric conditions such as schizophrenia, bipolar disorder, and addiction. Similarly, another report raises questions focused on genetic defects in mental illness and challenges related to implementing a metabolomics approach as a routine diagnostic tool in clinical laboratories in the context of neuropsychiatric disorders. [12,22].

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#### 4. Limitations of Omics as Surveillance Tool

Practically, there are several scientific pieces of evidence that support the premise that likely molecular connectivity results from interplay either between drug abuse and metabolomics aspects or metabolomics in mental illness. Currently, although all these omics studies as surveillance and monitoring tool are in effect, there is not a federally approved clinical method of using biomarkers to treat mental health disorders without valuational study using specific makers in the pre-clinical stage utilizing three different animal models. There have been multiple challenges that arose from the attempt to bring in clinical biomarkers into the clinical manifestation along with those ending up in therapeutic outcomes. These limitations are because of personal biases and the inadequacy of the clinical sample and its verification data due to lack of funding. Even with these challenges, many clinical trials from profit companies have started using preliminary biomarker results in stem cell technology using gene-editing technology as a prototype of patient care [22].

Additionally, efforts have been made to survey treat or manage mental health and its genetic effect with medications that are genetically coded but to a struggle. Ideally, more concrete biomarkers will be found which allow clinicians to easily identify the best pharmaceutical option for a patient prior to multiple trials. The average antidepressant takes 2-4 weeks to reach a therapeutic dose and every medication does not work the same for each person, which delays a patient's treatment while they try multiple drugs for 2-4 weeks [27].

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#### 5. Conclusion

Mental health appears as a new area of integration between mental illness and metabolic alteration through exposure which is tied to many known biological and environmental stressors, but drug abuse plays a major role as well considering the statistics from cognitive health including human behavioral intervention and alteration. [24]. Both mental health and drug abuse hold different landscapes of a metabolic effect due to genetic bias or heredity. Therefore it is the need to consider future diagnostic and surveillance including monitoring of drug or nutraceutical trials for highly sophisticated throughput studies or Omics platform such as the Psychiatome which is the integration of genomics, epigenetics, proteomics, transcriptomics, toponomics, metabolomics, and neuroimaging to analyze psychiatric disorders [5]. Also, one Omics application such as a microarray analysis, and metabolomics can be used to treat trauma-related disorders and substance abuse [24].

To further determine the unveiling of the molecule interaction circuit or interconnective molecule as disease determinants with functional identification while relevant cellular event processes, integrated Omics tools equipped imaging methodology could be considered to visualize the physiological or functional impairment and structural/conformational alteration of which genes include regulatory microRNAs are responsible for a disorder by looking at global gene expression profiles in tissues using animal models or patient samples [11]. In addition, the improvement of personal care (or individualized) systems facilitates communication utilizing genome bank and electronic medical records in rare disease repository data bank with regard to susceptible or mutation prone- genes we can create effective treatments and even design medication specific to an individual's experience with the disorder which we used for the model of metabolism alteration.

Interestingly, increasing scientific evidence supports the premise that molecular connectivity likely results from interplay either between drug abuse and metabolic alterations or between mental illness and metabolic alteration.

Overall, the future perspective of using the metabolomic platform sheds light on the venue from risk to resolution in the field of biomarker exploration, innovative treatment and the discovery of preventive measures, and evaluation of assessment procedures integrated in a clinical setting for the treatment of mental illness, and augment prevention of drug abuse. Advanced medicine with early molecular diagnostics is necessary to implement molecular dynamics and profiles reflect covering diversity and connectivity upon gene and individual-oriented environmental disease development looks promising to explore the new value of patient care ensure key determinants to environmental exposure and its visualization effect over metabolism with functional aspects interplay aligned with the microbiome and neural network and reward deficiency in the brain dynamics.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

The authors declare no conflict of interest.

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