



## Review article

## Current challenges and possible future developments in personalized psychiatry with an emphasis on psychotic disorders

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## ABSTRACT

A personalized medicine approach seems to be particularly applicable to psychiatry. Indeed, considering mental illness as deregulation, unique to each patient, of molecular pathways, governing the development and functioning of the brain, seems to be the most justified way to understand and treat disorders of this medical category. In order to extract correct information about the implicated molecular pathways, data can be drawn from sampling phenotypic and genetic biomarkers and then analyzed by a machine learning algorithm. This review describes current difficulties in the field of personalized psychiatry and gives several examples of possibly actionable biomarkers of psychotic and other psychiatric disorders, including several examples of genetic studies relevant to personalized psychiatry. Most of these biomarkers are not yet ready to be introduced in clinical practice. In a next step, a perspective on the path personalized psychiatry may take in the future is given, paying particular attention to machine learning algorithms that can be used with the goal of handling multidimensional datasets.

## 1. Introduction

The human brain is by far the most complex structure of the body. It is so exquisite we may still be far from fully understanding the way it functions, especially in regard to brain circuits that determine the human mind. Deviations of this tremendously intricate system from the normal function are often translated as psychiatric symptoms. It comes as no surprise that it is extremely challenging for a clinician to classify all existing manifestations of these deviations, in particular because defective brain circuits are always under influence of other factors, like healthy brain circuits, which are also different in different individuals [1]. The function of the brain is also altered, during the lifetime, by different molecular factors brought by epigenetics, stages of development and aging, and endocrine and immune systems. From the viewpoint of genetics, genes with pathogenic variants, associated with mental disorders, always interact with other genes, bearing functional, but not necessarily pathogenic variants. The overall result of the deviations from

normal functioning under additional influences is thus truly unique to each psychiatric patient.

Psychiatric disorders have the heaviest toll on population health, in terms of Years Lived with Disability (YLDs), compared to any other medical category [2, 3]. Despite the pressing need for improved standards of care, the currently existing traditional diagnostic criteria, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10), fail to reflect the actual biology behind mental illnesses [4, 5, 6, 7]. If we do not understand the nature of the pathological phenomena we are dealing with, it is hard to imagine how we will be able to efficiently treat and prevent these disorders.

This general informative review describes current difficulties in personalized psychiatry, followed by several examples of biomarkers of psychotic and other psychiatric disorders, including genetic biomarkers. These biomarkers, with exception of a few pharmacogenetic-guided decision support tools, have not been yet introduced in clinical practice. In

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In addition to the brief overview of the current status of clinical and biomedical research in psychiatry, the review gives a perspective on future developments, including the translation of scientific discoveries into clinical practice and machine learning algorithms that can be used with the goal of handling multidimensional datasets. The present review is different from previously published reviews on personalized psychiatry in three ways: (1) it is aimed at readers outside of the field of psychiatric research and is meant to be accessible to the general biological and medical community; (2) it gives examples of and discusses both genetic and phenotypic biomarkers, avoiding giving preference to one type of biomarkers over another; (3) contrary to other reviews dealing separately with biomarkers or with machine learning domain applications, the present review integrates both these aspects.

## 2. Current issues in psychiatry and possible solutions

### 2.1. Categorical classification systems in psychiatry are not based on etiology

Traditional diagnostic tools, DSM-5 and ICD-10, propose symptom-based categories into which we may “fit” the patients [6]. However, the actual clinical picture in each patient is more complex than the existing nosological entities: a patient may simultaneously “fit” into different diagnoses [8], present most but not all “required” signs and symptoms, and drift from one diagnosis to another. This may be explained in part by the technical difficulty diagnosing psychiatric illnesses, stemming from the absence of valid tests that can unambiguously indicate the diagnosis. However, insufficient power of existing diagnostic methods cannot be the only reason for these systematization difficulties. Molecular factors are shared between different nosological entities [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22] and, at the same time, within one nosological entity there is a great variability [23, 24, 25, 26, 27, 28, 29, 30]. For example, schizophrenia (SCZ), while sharing symptoms with other psychiatric disorders [31], is a questionable umbrella term incorporating etiologically and pathophysiologically distinct syndromes [32, 33, 34, 35]. In other words, the existing psychiatric diagnoses are too narrow and too broad at the same time [5, 36].

### 2.2. Research Domain Criteria

Despite the apparent complexity of the biologically informed and personalized approach in psychiatry, this approach seems particularly relevant to this branch of medicine [23, 24, 25, 28, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56]. As an answer to the existing demand, a new experimental framework in psychiatry was proposed in 2009 by an internal workgroup of the National Institute of Mental Health staff: Research Domain Criteria (RDoC) that adopt a personalized approach based on dimensions, rather than categories [4, 6, 7, 57, 58, 59]. RDoC is a research initiative aimed at informing future versions of diagnostic systems (ICD and DSM) [4, 6, 57, 58, 59]. According to the NIMH Strategic Plan, it is “a classification system based upon dimensions of observable behavior and neurobiological measures” (<http://www.nimh.nih.gov/about/strategic-planning-reports/index.shtml>). Although it is not designed as an independent diagnostic system aimed at replacing the current systems, nor it is fully developed at present, the arrival of RDoC seems timely, because it is about to develop a long-awaited etiology-based framework [6]. RDoC considers six domains that encompass several constructs, represented by different faculties of the human brain (<https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml>). Examples are social communication, cognitive control, and circadian rhythms. These constructs are perceived as dimensions, and the patient is thus characterized in this “multidimensional space”. Each construct is defined by seven units of analysis that can be applied to evaluate it. The units of analysis are defined by quantitative evaluations, such as levels of hormones, gene expression levels, neuroimaging, or neurocognitive tests. In this manner, a particular

faculty of the human brain is described as on a scale, ranging from “normal” to different degrees of “abnormal”.

RDoC principles have been put in action in clinical studies in order to define particular dimensions in groups of patients with different classical categorical diagnoses. For example, a continuum in severity of cognitive deficits was found when bipolar disorder (BD) type I and schizophrenic patients were characterized using the RDoC dimension “cognitive control” measured with a cognitive test and functional magnetic resonance imaging [60].

### 2.3. Biomarkers

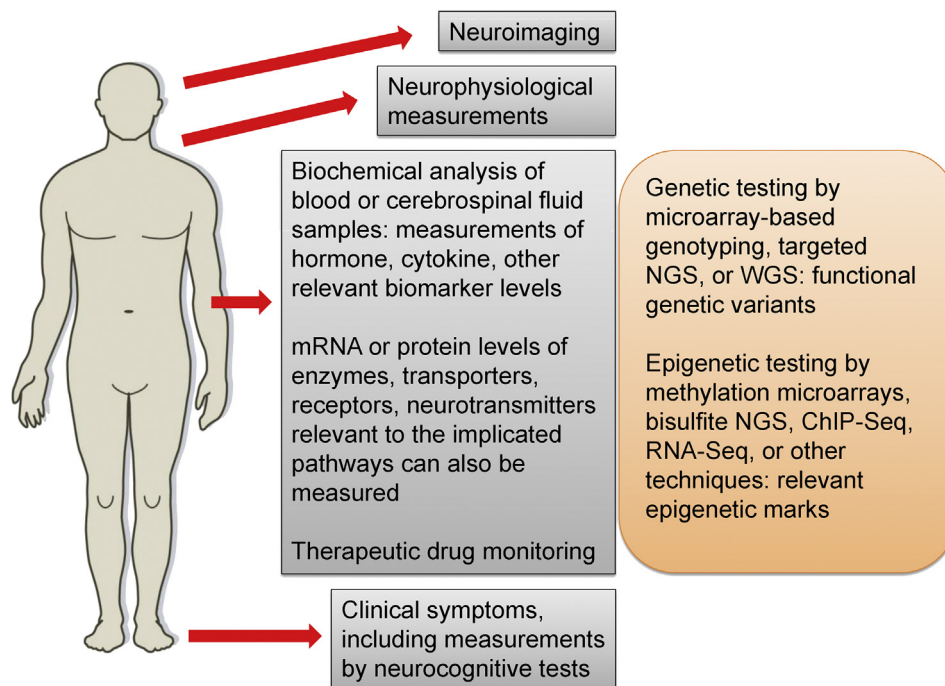
The framework of RDoC is just one potential path personalized psychiatry may take in the upcoming years. Another approach is based on a search for biomarkers of psychiatric disorders. According to the Biomarkers Definitions Working Group, a biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [61]. In other words, a biomarker is a relevant biological characteristic that can be unambiguously evaluated with a test [62, 63, 64] (Figure 1). An example is the blood glucose level in diabetes. Biomarkers do not answer to all questions about health and disease, but they indicate particular aspects of biological processes.

The quest for biomarkers in psychiatry has not been very successful [23, 24, 25, 28, 49, 51, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74]: as mentioned earlier, no biomarkers, with exception of a few pharmacogenetic-guided decision support tools, have been introduced in clinical practice. This might stem from the fact that researchers try to discover a biomarker that would be present in all or in the majority of patients with a particular “diagnosis”. Given that the current nosology in psychiatry might not reflect the actual molecular etiologies, the quest for unifying biomarkers in what is defined as SCZ or major depressive disorder (MDD) seems like an unachievable goal [6]. Although a minority of psychiatric cases, such as SCZ (9.9%) and MDD (2.8%), were found to be cases of autoimmune encephalitis [75, 76], that could be neoplastic or viral in its origin [77], the etiology of the vast majority of psychiatric cases cannot be determined with one clear agent and instead these disorders are considered a result of a very complex interaction of a myriad of molecular factors [78, 79].

This does not mean biomarkers do not apply to personalized psychiatry. Quite the opposite, it is crucial to discover actionable biomarkers that will inform us about the molecular basis of the illness. These biomarkers would act as pieces of a puzzle that constitute the entire clinical picture in one particular individual. The pieces would inform us about the precise pathological processes and indicate an appropriate treatment. Despite the difficulties, there have been studies that indicated a number of potentially actionable biomarkers in psychiatry [23, 24, 25, 28, 49, 51, 65, 66, 67, 69, 70, 71, 72, 73, 80, 81, 82, 83, 84]. Described in the next sections are only several examples of such biomarkers of psychotic and other psychiatric disorders, including genetic biomarkers, and therefore a brief overview of the existing body of knowledge. This brief list is not meant to name only fully studied and reliable biomarkers that are ready to be introduced into clinic, because at this point such biomarkers, with exception of few pharmacogenetic biomarkers [45, 85, 86, 87, 88], have not been discovered.

Epigenetics is another root cause of the processes taking place in the cell that is not necessarily defined by changes in the DNA sequence. The reader is referred to reviews dealing with the subject of epigenetic biomarkers in psychiatry [23, 89, 90, 91, 92], as the present review will describe only genetic aspects, mentioning epigenetic aspects only briefly.

It is also worth mentioning that the present review will discuss only the pharmacological approach to treatment. Apart from pharmacology and another widely-used treatment approach, psychotherapy, various brain stimulation (neuromodulation) techniques (electroconvulsive therapy [93], non-invasive methods [94, 95, 96, 97], and deep brain stimulation [94, 98, 99, 100, 101, 102, 103, 104]) as well as gene therapy



**Figure 1.** A possible case scenario of personalized approach in psychiatry. A number of biomarkers, including transcriptomic and proteomic profiling and response to medication, along with relevant genetic and epigenetic factors are considered for the following data analysis.

[105, 106] are potential approaches to treat psychiatric disorders. While some brain stimulation methods were approved for clinical use [96, 97, 107], gene therapy is an approach still limited to biomedical research laboratory settings, with the hope it will be translated into clinical settings sometime in the future.

### 3. Examples of potential phenotypic biomarkers of psychotic and other psychiatric disorders

Examples of potential neurophysiological, immune, and endocrine biomarkers are given below. Other proteomic [23, 49, 108, 109, 110], gene expression (transcriptomic) [20, 23, 49, 108], and neuroimaging [24, 73, 111, 112, 113, 114, 115, 116, 117, 118] biomarkers are additional important examples that are described elsewhere. These biomarkers have the potential to be used as diagnostic instruments and indicators of disease prognosis and treatment outcome (diagnostic, prognostic and predictive biomarkers, respectively [119]), but they have not yet been validated [23, 24, 25, 51, 64, 71, 72]. For these reasons, these potential biomarkers continue to be investigated in experimental settings either aimed at revealing molecular mechanisms behind them, or aimed at validating them as robust biomarkers.

#### 3.1. Neurophysiological biomarkers

##### 3.1.1. Mismatch negativity

The mismatch negativity (MMN) is a component of event-related potentials (ERP), measured with electroencephalography [25, 120, 121, 122]. MMN is a negative voltage deflection that is observed when among frequently presented standard auditory stimuli there is an infrequent deviant stimulus. This deflection is weaker in individuals with SCZ or those who later present psychotic symptoms [123, 124, 125, 126, 127, 128], which means that it can be used to identify high-risk individuals for preventive interventions. MMN is associated with poor functioning of patients in the community [129, 130, 131, 132, 133, 134] and reduced cognitive function in patients and healthy subjects [131, 132, 134, 135, 136, 137, 138].

These ERP deficits seem to be related to an N-methyl-D-aspartate (NMDA) receptor hypofunction [139, 140], because insufficient MMN can be corrected and clinical symptoms improved by treating schizophrenic patients with N-acetyl-cysteine that is subsequently converted to glutathione [141, 142]. Glutathione potentiates the NMDA receptor through its redox activity [143], in a similar manner NMDA receptor antagonists provoke psychotic symptoms [141]. NMDA receptor is a constituent of the postsynaptic density that is believed to be a hotspot of pathogenic alterations in a number of psychiatric disorders, such as SCZ, autism spectrum disorders (ASD), mental retardation, mood disorders, and obsessive-compulsive disorder (OCD) [23, 144, 145, 146].

This encephalographic measure appears to be an easy-to-use, cost-effective, reliable, and informative potential diagnostic instrument and an indicator of prognosis and treatment outcome for psychotic disorders [121]. It is also ready for use in large-scale multisite clinical studies of SCZ [147].

##### 3.1.2. Retinal anomalies

Other potentially actionable diagnostic and prognostic biomarkers in psychiatry are retinal anomalies, measured by an electroretinogram, including reduction of cone and rod wave amplitudes, detected in BD and SCZ patients [148]. In addition, these waves were studied using mouse strains with either increased or decreased/absent levels of expression of *GSK3 $\alpha$*  and *GSK3 $\beta$*  [149], whose protein products play a very important role in molecular pathways, implicated in psychiatric disorders, AKT/GSK3 and WNT [150, 151, 152]. In particular, the WNT pathway seems to be implicated in the pathogenesis of SCZ, ASD, and mental retardation [153, 154, 155, 156, 157, 158]. Expression levels of *GSK3 $\alpha$*  and *GSK3 $\beta$*  were inversely correlated with cone and rod wave amplitudes, which underlines the pathogenic role of *GSK3 $\alpha$*  and *GSK3 $\beta$*  excessive activity [149] that leads downstream to reduced levels of  $\beta$ -catenin in psychiatric pathology [150, 151, 152]. Furthermore, multiple retinal anomalies were observed in mouse models of decreased serotonin and increased dopamine functions that represent neurochemical pathologies described in MDD and SCZ, respectively [159]. The model relevant to MDD was Arg439His tryptophan hydroxylase 2 knockin, containing the analog

of the human mutation Arg441His that inactivates the serotonin-synthesizing enzyme and decreases brain serotonin levels by ~80% [160]. The model relevant to SCZ was dopamine transporter knockout that results in increased extracellular levels of dopamine in the striatum [161]. In the model of decreased serotonin function an increase in cone b-wave implicit time was observed, whereas the model of hyperdopaminergia was characterized by a decrease in rod sensitivity; these retinal anomalies may therefore be biomarkers of MDD and SCZ [159].

### 3.1.3. Prepulse inhibition

A further example of potential diagnostic instrument and indicator of treatment outcome is prepulse inhibition (PPI) of the startle reflex, a capacity of the brain to filter out irrelevant stimuli that is determined by the limbic cortico-striato-pallido-pontine circuitry [25, 162]. Because a muscle reflex is measured, it is a sensorimotor gating measure. PPI is insufficient in schizophrenic patients, which seems to explain the nature of hallucinations and delusions as insufficient filtering of irrelevant stimuli. PPI was also found to be impaired in patients with OCD and ASD [162]. It is important to note however that PPI should be eventually used in clinical settings in combination with other biomarkers due to its low sensitivity and specificity [25, 162].

## 3.2. Immune and endocrine biomarkers

### 3.2.1. Pro-inflammatory signaling factors

Multiple studies indicated anomalies in the immune system in patients diagnosed with MDD, BD, SCZ, and ASD [23, 26, 29, 51, 63, 64, 69, 163, 164, 165, 166, 167, 168, 169, 170]. The overall finding is deregulation of pro-inflammatory and anti-inflammatory factors, but the most consistent finding is an increase of pro-inflammatory cytokines and other immune signaling factors (Table 1). Examples are interleukin 6 (IL-6), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), C reactive protein (CRP), and the interferon  $\alpha/\beta$  (IFN- $\alpha/\beta$ ) signaling pathway components in MDD [49, 51, 171, 172, 173, 174]; IL-6, IL-1 $\beta$ , TNF- $\alpha$ , soluble TNF receptors 1 and 2 (sTNFR1 and 2), and CRP in BD [69, 70, 71, 163, 170]; IL-1 $\beta$ , IL-6, IL-12, TNF- $\alpha$ , and transforming growth factor  $\beta$  (TGF- $\beta$ ) in SCZ [165, 170, 175, 176, 177, 178, 179]; and sTNFR2, IL-4, IL-5, and IL-13 in ASD [180, 181]. It is not clear however whether the immune system deregulation in patients shares the etiology with mental disorders [182, 183, 184], for example, via the kynurenine pathway [23, 163, 185, 186, 187, 188], or is a consequence of a chronic illness [189, 190].

Clinical studies also indicated potential usefulness of these biomarkers in predicting treatment outcomes [191]. For example, baseline serum CRP levels in patients with MDD could predict antidepressant treatment response [192].

There are many ways to evaluate immune factors in blood serum and cerebrospinal fluid [193], examples being a multiplex immunoassay [166] and liquid chromatography tandem mass spectrometry [194].

### 3.2.2. Hypothalamic-pituitary-adrenal axis and insulin

The hypothalamic-pituitary-adrenal axis in MDD, BD, and SCZ is overly active [30, 50, 51, 195, 196], and the patients are afflicted with elevated cortisol levels [30, 51, 179, 195, 196, 197, 198, 199, 200] (Table 1). In addition, these patients are often diagnosed with insulin resistance, accompanied with hyperinsulinemia [199, 200, 201, 202, 203, 204, 205, 206, 207, 208]. Cortisol is produced by the adrenal gland in response to stress and is known to cause insulin resistance [209]. These endocrine abnormalities could share a common etiology with mental illnesses, because reduced stress tolerance was observed in psychiatric patients [196, 198]. Additionally, insulin resistance, that can result in type 2 diabetes, and hyperinsulinemia, that can result in hypoglycemia, both have a negative impact on the neuronal function [210, 211, 212].

Although endocrine biomarkers in psychiatry still await clinical validation, clinical studies indicate promising candidates, such as insulin levels in schizophrenic patients that may be predicting response to antipsychotic treatment and the time until patients in remission would relapse [213].

## 4. Examples of genetic studies relevant to personalized psychiatry

Single nucleotide polymorphism (SNP) genotyping is followed by statistical analyses of association between variants and phenotypes [21, 216, 217, 218, 219], including polygenic risk score analyses [217, 220, 221]. Despite impressive sample sizes and robust statistics, only a minority of these studies, unfortunately, is followed by functional assays for the associated variants, using *in vitro* and *in vivo* models [222].

Rare single nucleotide variants (SNVs) and small indels are discovered by sequencing [11, 12, 13, 157, 223, 224] and may be used to conduct population association studies. While rare and predicted to be deleterious protein-truncating and missense variants in 26 genes were found to be associated with ASD [224], at present, rare and predicted to be loss-of-function variants in just one gene, *SETD1A*, were found to be associated with SCZ [12]. No such genes were discovered in population association studies of other psychiatric disorders. The main reason for this lack of association with rare and deleterious variants is that psychiatric disorders are common and highly polygenic, so in order to detect association with rare variants, sample sizes exceeding what is presently used in genomic studies (10 000–130 000 cases) are needed [78].

Copy number variants (CNVs) are another category of rare variants of large effect on the pathogenesis and the reader is referred to other articles discussing the role of these genetic variants in psychiatry [225, 226, 227, 228].

These potential genetic biomarkers, with exception of a few pharmacogenetic-guided decision support tools, still awaits clinical validation and is not introduced in routine clinical practice. Same as in

**Table 1.** Examples of immune signaling factors and hormones that are increased in psychiatric patients.

Biomarker	Disorder	References
IL-1 $\beta$	BD, SCZ	[70, 71, 163, 165, 170, 175, 177, 214, 215]
IL-4, IL-5, IL-13	ASD	[181]
IL-6	MDD, BD, SCZ	[49, 51, 70, 71, 163, 172, 173, 174, 176, 177, 179]
IL-12	SCZ	[177]
TNF- $\alpha$	MDD, BD, SCZ	[49, 51, 69, 70, 71, 163, 172, 174, 177]
sTNFR1	BD	[69, 71]
sTNFR2	BD, ASD	[69, 180]
TGF- $\beta$	SCZ	[177]
CRP	MDD, BD	[49, 69, 70, 71, 173, 192]
IFN- $\alpha/\beta$ pathway	MDD	[171]
cortisol	MDD, BD, SCZ	[30, 51, 179, 195, 196, 197, 198, 199, 200]
insulin	SCZ	[30, 199, 200, 207, 213]

the previous section, below are given several examples of genetic biomarkers holding promise for future clinical use.

#### 4.1. Association studies

There have been a number of association studies aimed at discovering genetic biomarkers in psychiatry [27, 28, 49, 50, 51, 229]. Despite the impressive amount of data, the results obtained are often inconsistent [27, 28, 49, 51]. This could be explained by the fact that symptom-based diagnostic categories used to group patients do not reflect biological reality [6].

One of these genetic studies confirmed association of interacting *GSK3 $\beta$*  and fragile X mental retardation-related protein 1 (*FXR1*) [230] with the level of mania in acute periods and depression in stabilized periods in BD patients [231]. Another study revealed the haplotype A-G-T in the promoter of the IL-1 $\beta$  gene that is associated not only with higher levels of expression of this cytokine in the dorsolateral prefrontal cortex (DLPFC) and a reduction of the total grey matter volume in schizophrenic patients and healthy controls [215], but also with transition to psychosis [214], which makes it a potential prognostic genetic biomarker. A further study investigated association between 1536 SNPs in 94 candidate genes and 16 primary and secondary neurophysiological and neurocognitive measurements in patients with SCZ [232, 233]. SNPs in 40 genes, including  $\alpha$ -catenin *CTNNA2* [234] and neuregulin *NRG1* [235], were found to be associated with some of these measurements. Also, association between *NRG1* and positive symptoms of SCZ [236], smooth pursuit eye movements [237], and parameters of an ERP component P300 [238] was revealed. Further studies showed association between the  $\alpha 7$  nicotinic receptor gene *CHRNA7* and the neurophysiological biomarker sensory gating/P50 suppression, but not with SCZ *per se* [239, 240, 241]. The SNP rs1344706 in the zinc-finger protein (ZNF) gene *ZNF804A*, associated with BD and SCZ in genome-wide association studies (GWAS) [242], was also associated with P300 parameters [243]. Another study estimated association between functional magnetic resonance imaging measurements and the same SNP [244]. This study revealed disturbed connectivity in the DLPFC, hippocampus, and amygdala in healthy carriers of the associated allele, a finding that recapitulated results in psychiatric patients. Similar results were obtained for neuroimaging data in BD, MDD, anorexia nervosa, attention deficit hyperactivity disorder (ADHD), ASD, and SCZ [19, 220].

#### 4.2. Functional studies

The importance of functional studies is paramount because they are the most convincing evidence the link between a genetic variant and a biomarker is real. Statistical test results, no matter how significant they are and how many times replicated in independent samples, do not prove there is a cause and effect relationship. In other words, genetic biomarkers with evidence confirmed only by statistical association should be used in clinic to make decisions with great caution, because in such case we still do not understand the precise molecular mechanisms leading from a given genetic variant to the measurable phenotype. Meanwhile, functional alleles in several individual genes, discovered by sequencing or statistical association, were studied in detail, and results indicate particular pathological processes determined by these variants. Three examples are given below.

##### 4.2.1. Kalirin

*KALRN*, coding for a Rac1 guanine nucleotide exchange factor kalirin, was found to bear a rare variant p.Asp1338Asn in two siblings, one with SCZ and the other with MDD and drug and alcohol addiction [245]. The presence of the variant was correlated with reduced cortical volume in the superior temporal sulcus in these patients. The mutation is found in the protein domain that catalyzes activation of the GTPase Rac1 and

reduces this activation. Overexpression of the mutated variant in mature cortical pyramidal neurons resulted in abnormalities of dendritic spines. Furthermore, a murine model with reduced expression of the gene showed a reduced number of neurons in the murine brain region corresponding to the human superior temporal sulcus [245].

##### 4.2.2. G protein-coupled receptor kinase interacting ArfGAP 1

Another rare variant p.Arg283Trp in G protein-coupled receptor kinase interacting ArfGAP 1, *GIT1*, was discovered in four unrelated patients with SCZ, in addition to six other rare coding variants in this gene in schizophrenic patients [246]. *GIT1* is active in both presynaptic and postsynaptic neurons and in both excitatory and inhibitory synapses [247, 248, 249, 250, 251]. This protein controls synaptic vesicle dynamics, dendritic spine growth and localization of neurotransmitter receptors. As was demonstrated by *in vitro* studies using human cell lines, including hippocampal neurons, the variants resulted in reduced activation of p21 protein (Cdc42/Rac)-activated kinase 3 (PAK3) and mitogen-activated protein kinase (MAPK), a finding correlated with synaptic deficits [246].

##### 4.2.3. Complement component 4

Two paralogous genes of complement component 4, *C4A* and *C4B*, are associated with SCZ [217]. The allele that is characterized by two long (presence of a human endogenous retroviral insert) copies in tandem of *C4A* is associated with the greatest risk of SCZ [222]. This allele is also associated with the highest level of *C4A* expression in the brain, a finding also true for schizophrenic patients when compared to controls. This gene is expressed in basically all compartments of human neurons: synapses, dendrites, axons, and cell bodies. In a murine model, C4 mediated synapse elimination (pruning) during postnatal development [222], a molecular mechanism believed to determine, when excessive, the pathogenesis of SCZ, a neurodevelopmental disorder with an insufficient number of synapses [252, 253, 254].

#### 4.3. Pharmacogenetic studies

An important number of studies reported the statistical association of genes with response to treatment by antidepressants, mood stabilizers, antipsychotics, and antiepileptics, the results that were also supported by some functional studies [28, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 56, 255, 256, 257, 258].

##### 4.3.1. Cytochrome P450 enzymes

The cytochrome P450 (CYP) enzymes are known drug-metabolizing enzymes that can determine drug concentration in the blood, depending on their genotype, and therefore drug availability, a pharmacokinetic aspect. These biomarkers thus indicate both the drug efficacy and safety. One gene is *CYP2D6* whose protein product metabolizes 40% of antipsychotics, as well as drugs for ADHD and various antidepressants, such as tricyclics or tetracyclics, that are serotonin and/or norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors [44, 45, 259]. The gene is characterized by a number of functional genetic variants that determine the catalytic activity of the enzyme. In particular, alleles that determine "poor metabolizers" are associated with increased availability of drugs such as haloperidol and risperidone and, as a consequence, higher rates of some undesirable side effects, such as tardive dyskinesia and weight gain [259]. Other CYP genes, such as *CYP2C19*, have analogous effects on pharmacokinetics [44, 45, 259]. *CYP2D6* and *CYP2C19* genotyping was shown to be cost-effective [260, 261] and is already available in some commercial pharmacogenetic tests [45, 85, 86, 87, 88], although considerable improvements of these tests are still needed, due to the fact that the testing results do not always agree with each other and the test design does not always follow reporting recommendations [262, 263].

#### 4.3.2. Major histocompatibility complex proteins

Pharmacodynamic genetic biomarkers *HLA-B\*15:02* and *HLA-A\*31:01* indicate adverse reactions to carbamazepine [257, 264, 265], an antiepileptic drug also used to treat BD and other psychiatric disorders [266]. These biomarkers thus indicate the drug safety. *HLA-B* and *HLA-A* are genes coding for the major histocompatibility complex proteins that take part in the presentation of antigens to T-lymphocytes. The allele *HLA-B\*15:02* codes for a protein with a particular three-dimensional configuration that allows binding carbamazepine; the result of this binding is a cytotoxic immune reaction [267, 268]. A similar mechanism may take place in case of *HLA-A\*31:01*. As a consequence, the carriers of these alleles are susceptible to develop severe cutaneous reactions [264, 265, 269, 270, 271], such as Stevens–Johnson syndrome and toxic epidermal necrolysis. Genotyping *HLA-B* and *HLA-A* genes in patients before prescribing carbamazepine is therefore advised in order to alleviate these life-threatening adverse reactions [272, 273, 274] and was shown to be cost-effective [260]. As a result, genetic testing of these alleles is currently available [274, 275], although, as mentioned above, the commercial tests need major improvements [263].

#### 4.3.3. Glycogen synthase kinase 3-beta

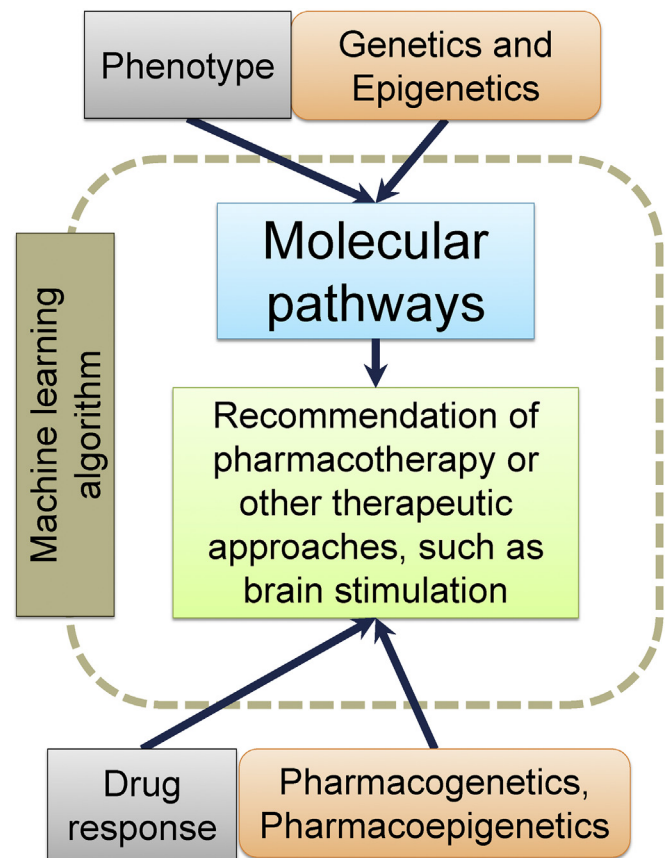
A potential pharmacodynamic genetic biomarker is the functional SNP rs334558 [276] in the gene *GSK3β* [150] coding for glycogen synthase kinase 3-beta that is associated with response to antidepressant medication in patients with depressive disorders [277, 278] and lithium treatment in patients with BD [279, 280, 281, 282, 283, 284]. The variant rs334558, found in the promoter, determines the expression level of *GSK3β*; in particular, the allele T is associated with 1.4-fold increased transcriptional strength, compared to the ancestral allele C, apparently because the nucleotide T creates a new binding site for the transcription factor AP4 [276]. The SNP rs334558 could therefore be viewed as a pharmacogenetic biomarker for mood disorders [53, 258], but it should be used in conjunction with other biomarkers due to its low specificity [278]. This potential predictive biomarker should be further studied in clinical settings, before a reliable genetic test is developed.

### 5. A possible route that personalized psychiatry may take in the future

#### 5.1. Translation of scientific discoveries into clinical practice

Genetic, epigenetic, and phenotypic data may be used to determine the appropriate treatment for an individual. The genotyping in clinic could be based on microarray technologies, if only previously known genetic variants are considered, and sequencing may be based on next-generation sequencing (NGS) technologies. NGS can be either whole genome (WGS), or targeted to all or particular exons and regulatory sequences. Epigenetic testing may be performed by methylation microarrays, bisulfite NGS, chromatin immunoprecipitation sequencing (ChIP-Seq), RNA-Seq, or other relevant techniques. All relevant, informative biomarkers, such as neurophysiological, neuroimaging, and biochemical measurements, should be sampled. In addition, transcriptomic and proteomic profiling could be made, using appropriate gene expression microarray, RNA-Seq, protein microarray, or mass spectrometry techniques (Figure 1). Examples of early attempts to apply such multidimensional analyses to sets of biomarkers in order to better characterize patients include a study that combined genetic, neuroimaging and clinical biomarkers thus defining three subtypes of schizophrenic patients [285].

The most important information to be deduced from biomarkers is molecular pathways implicated in the pathogenesis in relevant cell types [15, 41, 286] (Figure 2). The pathways encompass all DNA, RNA, and protein interactions in the cell, from gene expression regulation to exocytosis. Genetics and epigenetics will indicate the possible etiology and information drawn from the sampling of phenotypic biomarkers will indicate the phenotypic consequences; between the two are molecular



**Figure 2.** Machine learning algorithm applications. Multidimensional data may be analyzed by a machine learning algorithm that integrates the genotype, epigenotype, and phenotype of an individual to extract information about molecular pathways implicated in the pathogenesis. Genetic, epigenetic, and therapeutic drug monitoring data from the individual is also used to choose the safest and most efficient pharmacological agents, and, at the same time, information about the pathways is used to select the most appropriate pharmacological agents. Alternative therapeutic approaches, such as brain stimulation techniques, can also be chosen.

pathways that are altered. An example of the pathway is the NMDA receptor signaling complex found in the postsynaptic density of glutamatergic neurons that is believed to be one of the hotspots where pathogenic events resulting in a number of psychiatric disorders take place [144].

In order to create a link between genetics, epigenetics, phenotype, and molecular pathways, it is crucial to carefully study all existing functional genetic variants and epigenetic marks that can result in significant alterations in protein or non-coding RNA function. We are still far from this complete knowledge, as the genetic and epigenetic basis of the vast majority of biomarkers is still unknown, and for the vast majority of discovered genetic variants and epigenetic marks, statistically associated with mental illnesses, there are no described pathogenic molecular mechanisms. Functional studies revealing the link between genetic, epigenetic, and phenotypic biomarkers are therefore essential for the development of a personalized approach in psychiatry [78]. Novel approaches, such as multiple assays of variant effects [287] and integrative systems like ClinGen [288], could be useful in establishing a list of actionable variant candidates.

When the picture of altered molecular pathways is drawn, it will be possible to choose the most correctly targeted therapeutic approach, including pharmacotherapy, i.e. biologically active molecules that will be able to correct faults in the pathways in the most efficient way. At this point, pharmacogenetics and pharmacoepigenetics will be taken into

account, because genotyping or sequencing will indicate the patient's pharmacokinetic and pharmacodynamic particularities, which will help choosing the treatment correctly. At the same time, therapeutic drug monitoring [289] should be applied in order to integrate pharmacogenetic and pharmacoeigenetic parameters with actual clinical measurements (Figures 1 and 2). Again, we are still far from full understanding of all aspects of pharmacogenetics and pharmacoeigenetics, and, because we still have not fully understood the existing pathogenic mechanisms behind mental illnesses, we have not discovered all relevant pharmacological agents. Functional pharmacogenetic, pharmacoeigenetic, and drug development studies are therefore also essential for the advancement of a personalized approach in psychiatry. In addition, not all pharmacogenetic (or pharmacoeigenetic) testing in clinic has yet been shown convincingly to be cost-effective [261, 290], so more prospective studies evaluating cost-effectiveness, together with development of new cost-effective treatment schemes, are needed. Furthermore, considerable improvements of these commercial tests are warranted, because the testing results do not always agree with each other, and the test designs do not always follow reporting recommendations [262, 263].

## 5.2. Data analysis using machine learning algorithms

The scenario described above actually signifies a tremendous amount of multidimensional, heterogeneous (and often sparse) data that will be very challenging to analyze. In particular, it will be necessary to take account of all other genetic and epigenetic factors, not only the pathogenic ones. To accomplish this goal, it seems appropriate to apply data-driven analysis methods from machine learning domain [291, 292, 293], including deep learning [294], as their power to translate complex pattern discovery in large and varied data into clinically relevant practices has been recently demonstrated in several neuroscience research projects, including PsychENCODE [295, 296, 297]. Since these approaches are generally agnostic as to the underlying mechanisms, they facilitate both the *de novo* discovery and statistical modeling of molecular pathways in relevant cell types. Thus, in order to generate the most justified answer in a form of a treatment strategy, such models incorporate biomarker measurements, therapeutic drug monitoring and electronic health records (Figure 2).

### 5.2.1. Supervised learning

Machine learning may be supervised or unsupervised. Supervised learning (e.g. decision trees, k-nearest neighbor algorithm, support vector machines, some of neural-network algorithms) is the machine learning task type associated with learning functional relations based on input-output data pairs (also called features versus target variables) [298]. By training on example pairs, the algorithm infers a function which allows predicting the best-possible outcome (i.e. a target variable) for mapping a new unseen input data point (i.e. a single patient).

Supervised machine learning may be associated with several diagnostic applications, such as prevention and early diagnosis of mental health issues [299], exemplified by measurements of symptom progression in individuals at ultra-high risk for developing psychosis based on magnetic resonance imaging (MRI) data [300, 301]. This technique can also be used for diagnosis confirmation. For example, 70% of BD patients are misdiagnosed, most often with MDD [302, 303]. This problem may be solved by applying the support vector machine, a multivariable supervised learning task and a sensitive classification algorithm, to MRI scans of patients with BD and MDD. This classification algorithm achieved an accuracy approaching 80% in differentiating the two categories of patients [304].

Another promising application for supervised machine learning in psychiatry is long-term clinical prognoses, in particular, with the help of electronic health records (EHRs) [305]. EHRs can be also used for extraction of RDoC dimensions that demonstrated accurate predictions regarding length of hospital stay and hospital readmission [306]. A multivariate pattern recognition study of MDD which used a combination

of clinical data and structural/functional MRI indicated that different disease trajectories, i.e. chronic, improving, and fast remission, could be discriminated with accuracies near 70% over two-month period [307]. Similar results of the functional outcome prediction over four weeks and over a year have been obtained for patients with first-episode psychosis, with accuracies surpassing 70% [308]. These applications can potentially be extended for predicting remissions, relapses, symptoms severity and quality of life in general.

Another issue which can be successfully solved by supervised machine learning algorithms is the determination of optimal treatment and dosage. Current success rate of treatment choices is dramatically low: only one third of individuals with a mental disorder who receive either drug treatment or psychotherapy fell into the category of 'at least minimally adequate treatment' [309]. Examples of successful supervised machine learning applications include predictions of clinical remission in response to drug treatments with escitalopram, citalopram, or sertraline in MDD patients [310, 311]. In these studies predictive models were generated from patient-reported clinical data [311] or behavioral tests of cognitive and emotional capacities [310]. An additional study also found that pre-treatment electroencephalogram measurements can be used for estimating response to antipsychotic treatment with clozapine in schizophrenic patients with total classification accuracy of 81.4% [312]. A further useful application for predictive modeling is assessment of drug side effects and of their severity. For example, three classification algorithms, i.e. artificial neural-network, support vector machine, and logistic regression, predicted metabolic syndrome in SCZ and schizoaffective disorder patients treated with atypical antipsychotics with accuracies of about 80% [313].

### 5.2.2. Unsupervised learning

As mentioned earlier, nosological classifications of psychiatric disorders in DSM and ICD need to be revised. All kinds of data from genomics and circuits to behavior and self-reports may be used to provide a new classification representing both underlying molecular basis of disease and existing clinical groups of patients. Since unsupervised machine learning, including cluster analysis (e.g. k-means, affinity propagation and DBSCAN algorithms), finds hidden patterns in data, it can be used for re-working existing mental health nosological systems [314, 315, 316, 317, 318]. Importantly, cluster analysis should be used in combination with dimensionality reduction techniques that transform a high-dimensional dataset into a smaller one [315, 319]. Cluster identification may also be based on the provisions of the RDoC initiative [315, 318]. Examples of applications include analysis of neuroimaging and physiological recordings that revealed three subtypes of ADHD with different types of emotional regulation labeled as mild, surgent and irritable [316]. Also, clinical characterization using cognitive and electrophysiological data of schizophrenic [317] and cognitive and neuroimaging data of BD [318] patients suggested distinct biologically validated subtypes of these disorders.

### 5.2.3. Limitations of machine learning in psychiatry

Although machine learning approaches are effective in application to clinical computational psychiatry, that is, in stratifying individuals in reference to diagnostic, prognostic, and treatment decisions, there are pitfalls and obstacles which also need to be examined carefully. Obvious limitations for deployment of state-of-the-art algorithms for psychiatric care are probably the size of available datasets, their heterogeneity, insufficient phenotypic annotation and incomplete medical records. Compared to other non-medical domains where, as it has been demonstrated, the sufficient predictive power for deep learning can be achieved if a sample size exceeds  $10^6$  samples [320], the typical cohort size in psychiatric research is far less than this threshold. Also, there are very few studies where all elements of the data triad (i.e. genotype, epigenotype, and phenotype) essential for understanding the disease trajectories and clinical guidance development are available. Furthermore, the confounding influences of different experimental protocols, standard

operating procedures, standards of care, cohort and population biases may contribute to inflated prediction performance and irreproducibility of the results, thus highlighting the importance of accurate accounting for confounding variables in machine learning applications for mental health research.

Last but not least, application of many machine learning tools and more importantly interpretation of results (e.g. why a sample is classified and how a model works) require substantial expertise and are frequently opaque to clinical researchers and clinicians. This creates a major barrier in the translation of statistical machine learning methods into routine clinical practice, which emphasizes the importance of educational initiatives that facilitate knowledge exchange between clinical researchers, experimentalists and data scientists.

## 6. Conclusions

This review described current challenges and possible future developments in psychiatry. The description of the multidimensional approach was intentionally simplified: epigenetic aspects and other therapeutic approaches, such as brain stimulation techniques, were only briefly mentioned. But, if personalized medicine in psychiatry one day becomes reality, genetic (including functional common SNPs, rare SNVs, as well as CNVs), epigenetic, and phenotypic biomarkers, pharmacology, psychotherapy, brain stimulation techniques, and gene therapy must all be taken into picture with the goal of translating scientific discoveries into clinical practice. Machine learning algorithms will be the only possible way to analyze these multidimensional datasets, in order to extract meaningful information from them. In this sense, psychiatrists will have to learn to work with these algorithms, and one of the roles of a psychiatrist in the process of determining the diagnosis will be to confirm the choices and treatment recommendations, made by the machine.

In order to make this scenario possible, functional studies aiming at understanding molecular networks implicated in the pathogenesis and response to treatment are of paramount importance [78]. Further development of new methods, allowing multiplex functional studies, is therefore needed [287, 321]. This research will make much more sense if sets of biomarkers or RDoC dimensions are considered, instead of the presently existing categorical nosological entities.

## Declarations

### Author contribution statement

Anastasia Levchenko: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Timur Nurgaliev: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Alexander Kanapin, Anastasia Samsonova: Analyzed and interpreted the data; Wrote the paper.

Raul R. Gainetdinov: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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### Competing interest statement

The authors declare no conflict of interest.

### Additional information

No additional information is available for this paper.

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