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Tailoring antidepressant therapy based on genetic profiles: Review

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***Abstract*---**Background: Depression is a substantial public health concern that impacts millions of individuals globally. The wide range of symptoms and manifestations of depression emphasizes the need of tailoring treatment methods to each individual, which includes adapting antidepressant prescriptions accordingly. Genetic factors contribute to depression and its association with other psychiatric and non-psychiatric illnesses, highlighting the need of a thorough assessment that encompasses psychopathology, physical health, and genetic variables. Aim of Work: This research aims to highlight the significance of customized therapy in the management of depression, taking into account hereditary variables, metabolic abnormalities, and inflammatory indicators. The research also seeks to emphasize the potential use of genotyping in directing the selection of antidepressants and making dose changes for people with altered metabolism. Methods: The research entails examining previously published works on the genetic factors related to depression, the influence of inflammatory and metabolic abnormalities in its development, and the possible advantages of genotyping in the treatment of antidepressants. The research also examines the incorporation of genetic information, such as the tendency to develop cardio-metabolic illnesses due to several genes, together with non-genetic risk factors to improve treatment results. Results: The findings of the research emphasize the significance of tailoring the treatment of depression to each individual, taking into account their specific genetic variants, metabolic abnormalities, and inflammatory indicators. Performing genotyping of CYP2D6/CYP2C19 variations may assist in determining the most suitable antidepressant options and necessary dose modifications for individuals with modified drug metabolism. Incorporating both genetic and non-genetic risk variables may enhance the ability to identify people who are susceptible to medication-related adverse effects. Conclusion: In summary, personalized medicine shows the potential to enhance the treatment results of depression by taking into account individual genetic profiles

and metabolic anomalies. By genotyping and combining genetic data with other risk factors, it is possible to improve the personalization of therapy and optimize the selection of antidepressants, leading to improved results for patients.

***Keywords*---**Major depressive illness, Antidepressant drugs, Genetics, Precision medicine.

Introduction

The global prevalence of depression is estimated to be 322 million people, with an 18.4% increase seen between 2005 and 2015. This rise may be attributed, in part, to the higher incidence of depression among those aged 55-74 years. Depressive disorders are the leading cause of non-fatal health loss worldwide, accounting for 7.5% of all years lived with disability in 2015, which amounts to nearly 50 million years lived with disability. Depression is a significant factor in suicide, leading to the loss of one life every 40 seconds worldwide [1].

Antidepressants are the primary choice for treating moderate to severe major depressive disorder (MDD) [2]. However, about one third of patients have symptom relief after the first antidepressant therapy, while another third do not achieve remission even after trying repeated antidepressant therapies [3]. The current prescribing guidelines lack sufficient information on techniques to tailor antidepressant treatment, typically leading to a limited number of alternatives being prescribed. The primary objective of MDD therapy is to enhance remission rates and thus promote recovery. This may be achieved by the implementation of personalized prescription, which has been linked to improved functioning and a decreased likelihood of experiencing depressive relapse [4]. The extensive array of antidepressant medications, consisting of approximately 40 compounds, poses challenges in acquiring comprehensive knowledge regarding their pharmacological properties and the existing scientific literature. Consequently, clinicians would greatly benefit from an easily accessible and practical guideline that facilitates the evaluation of key criteria for personalized prescription.

Prior evaluations have offered recommendations about the customization of antidepressant selection, taking into account the specific symptom profile of the individual, as well as factors such as drug tolerance, personal and family medical history, presence of other medical or mental conditions, and concurrent drugs [5]. Nevertheless, there is a dearth of literature that provides a comprehensive integration of clinical and genetic data to assist in determining the most suitable antidepressant for each person. The variance in treatment response and side effects between individuals is partially influenced by genetic variation, since research has shown it to be heritable [6]. Various symptom patterns were found to have partially distinct genetic profiles and varying degrees of overlap with psychiatric and immune-metabolic traits [7-9]. This suggests the possibility of a connection between the genetic factors that influence the development of Major Depressive Disorder (MDD) and its clinical presentation, as well as the genetic factors that affect the response to antidepressant medications. Thus, clinical symptoms may be read as indications of the specific genetic elements implicated

in the development of a disease and can help choose the most appropriate therapy, going beyond just prescribing an antidepressant that addresses the individual's clinical symptoms. This implies that it is feasible to expand the fundamental assessments used to choose which antidepressant to recommend, without the need for any genotyping.

Although there is no conclusive evidence, it is presently recommended to perform genotyping of polymorphisms in cytochrome P450 (CYP450) genes in patients who have not responded well or tolerated at least one prior medication [10]. Following the discussion on interpreting individual symptom profiles and utilizing CYP450 genotyping to customize antidepressant prescriptions, this review will explore the potential application of genome-wide data. Genome-wide data refers to a genotyping technology that has become affordable and widely available, not only in research settings but also as a direct-to-consumer product. This technology provides information on ancestry, health conditions, and genetic-based recommendations for lifestyle choices [11]. By early 2019, over 26 million individuals had used at-home DNA testing, indicating the increasing need for healthcare professionals to provide appropriate counsel to consumers seeking to understand the credibility and potential health consequences of such findings. The use of clinical and genetic information to customize therapy in Major Depressive Disorder (MDD) is given in a systematic manner that reflects their order of importance and makes it easier to implement them in clinical practice.

Aim of Work

The objective of this study is to emphasize the need of personalized treatment in the control of depression, including genetic factors, metabolic irregularities, and inflammatory markers. The study aims to highlight the possible use of genotyping in guiding the selection of antidepressants and adjusting dosage for individuals with modified metabolism.

Procedures for Implementing Precision Medicine In The Field Of Psychiatry
Step 1: Creating an Individual Symptom Profile based on Clinical and Genetic Factors

The unique profile of depressive symptoms has been proposed as a significant factor in determining the appropriate choice of antidepressant. This is because various antidepressants possess distinct pharmacological characteristics, resulting in variations in the most prevalent side effects and the symptoms they target. This topic was extensively examined in a previous review [5]. In this review, we explore specific instances that illustrate the correlation between the clinical-pharmacological and genetic viewpoints on depressive symptom profiles (Figure 1). These instances represent situations where selective serotonin reuptake inhibitors (SSRIs), which are typically the preferred treatment for major depressive disorder (MDD), may have a reduced likelihood of achieving positive outcomes [12].

The significance of evaluating and addressing immune-metabolic abnormalities in individuals with MDD who have atypical neurovegetative symptoms

The first example is to individuals diagnosed with Major Depressive Disorder (MDD) who exhibit symptoms such as increased weight and hunger, as well as excessive sleepiness, which are referred to as reversed neurovegetative symptoms. To minimize the likelihood of weight gain, it is recommended that clinicians steer clear of antidepressant medications that have anti-histaminergic (such as mirtazapine), anti-5-HT2C (serotonin receptor 2C) (such as mirtazapine and paroxetine), and anti-alpha-adrenergic effects (such as tricyclic antidepressants or TCAs) [13]. Additionally, it is advisable to refrain from using antidepressants that have anti-cholinergic (such as TCAs) and anti-histaminergic effects in order to prevent exacerbation of hypersomnia [5].

Biologically, genetic studies indicate that individuals with Major Depressive Disorder (MDD) who have reversed neurovegetative symptoms have a greater genetic similarity to immune-metabolic features compared to patients who do not have these symptoms. Specifically, research has shown that individuals exhibiting these unusual symptoms of depression have a greater genetic similarity to the genetic variables that influence C-reactive protein (CRP), body mass index (BMI), and triglycerides [7-9]. The existence of the symptom of weight gain during depression seems to be the primary factor influencing these outcomes. Being overweight or obese has been linked to an increased risk of Major Depressive Disorder (MDD) and is also thought to contribute to treatment-resistant depression (TRD) [14,15]. This may be due to the activation of pro-inflammatory and oxidative processes, as well as disruptions in dopaminergic neurotransmission [16]. Consequently, patients who experience neurovegetative symptoms in the opposite direction, such as weight gain, should undergo an assessment to determine if they have immune-metabolic changes (such as elevated levels of CRP, cholesterol, triglycerides, and glucose) and other risk factors for cardio-metabolic disorders (such as hypertension). These factors are likely to play a role in both the development of depressive symptoms and the presence of other medical conditions in this group. It is essential to include the prevention and treatment of immune-metabolic abnormalities as a crucial aspect of therapy. This is necessary not only for improving physical health but also for achieving a full remission of depressive symptoms. Notably, drugs that have been authorized for treating metabolic disorders, such proliferator-activated receptor (PPAR) agonists and statins, have been shown to possess anti-inflammatory, neurotrophic, and depressive properties.

Four open-label studies and three out of four randomized controlled trials (RCTs) have shown that the PPAR agonists pioglitazone and rosiglitazone had antidepressant benefits in individuals with severe depression [17]. Preliminary randomized controlled trials (RCTs) suggest that statins may have additional antidepressant benefits when taken in conjunction with selective serotonin reuptake inhibitors (SSRIs). There is a favorable correlation between BMI and CRP levels, which were shown to be greater in TRD compared to depression that responds to therapy [19]. Inflammation is linked to reduced dopaminergic neurotransmission, and dopamine, in turn, controls the immune system.

Additionally, under pro-inflammatory conditions, the metabolism of tryptophan shifts from producing serotonin to generating the neurotoxic metabolite kynurenine. Consistently, the use of a combination of bupropion (a dopamine reuptake inhibitor) and an SSRI (selective serotonin reuptake inhibitor) resulted in reduced depression symptoms compared to using just an SSRI in patients with high levels of CRP (C-reactive protein) at the beginning of the study [20].

Furthermore, studies have shown that pramipexole, a dopamine agonist known to be effective in treatment-resistant depression (TRD), has the ability to suppress the synthesis of interleukin 17 (IL-17) [21]. Thus, it is advisable to prioritize antidepressants that have dopaminergic action over serotonergic antidepressants for this particular set of individuals. Another category of medications being studied consists of compounds that specifically target inflammatory factors. A randomized controlled trial (RCT) discovered that the drug infliximab, which inhibits tumor necrosis factor (TNF), was successful in decreasing depressive symptoms in treatment-resistant depression (TRD) when the initial concentration of C-reactive protein (CRP) was higher than 5 mg/L [22]. It is crucial to keep in mind the anti-inflammatory benefits of physical activity, which have been shown to be particularly advantageous in individuals with elevated levels of TNF-α at the beginning of the study [21].

MDD with melancholic symptoms is characterized by impairments in the brain's reward system and a shared hereditary basis with schizophrenia

The symptoms of melancholic depression, such as anhedonia, weight/appetite loss, sleeplessness, and psychomotor abnormalities, are important factors to consider while determining the appropriate therapy for Major Depressive Disorder (MDD). Anhedonia is a condition defined by a widespread and unresponsive reduction in the ability to feel or anticipate pleasure. It is commonly linked to a poor response to antidepressant medications, especially SSRIs, and may endure as a lingering symptom. For patients with depression who experience a lack of pleasure in activities, doctors may contemplate therapy approaches such as behavioral activation, physical exercise, and/or a combination of antidepressants (preferably those with dopaminergic or noradrenergic effects) or augmentation techniques [23].

In line with the theory that dopamine plays a crucial role in processing rewards, variations in the gene responsible for the dopamine D2 receptor (DRD2) and the gene responsible for the metabotropic glutamate receptor GRM5, which is linked to a decrease in dopamine levels in the striatum, were shown to be related with anhedonia [24]. Studies have shown that anhedonia and other symptoms associated with melancholic sadness have hereditary variables in common with schizophrenia and alcohol use. In a separate investigation, a strong genetic predisposition for specific variations linked to schizophrenia was found to be linked to both a lack of positive response to antidepressant medication and a tendency towards more frequent episodes of melancholic major depressive disorder (MDD) [26]. This suggests that the genetic regions associated with schizophrenia may play a role in both the likelihood of experiencing melancholic symptoms and the effectiveness of treatment. However, it is important to note that these findings do not establish any causal relationships, and further

research is needed to determine the presence and direction of such relationships. Nevertheless, our findings endorse the suitability of exploring other therapeutic approaches in individuals exhibiting melancholy symptoms, as previously proposed. The coexistence of major depressive disorder (MDD) and alcohol use disorders is linked to worse clinical outcomes [27].

Previous research has demonstrated that symptoms of melancholic depression, specifically psychomotor disturbances, are more commonly observed in individuals with substance use disorders compared to other subtypes of depression [28,29]. However, it is important to consider that other factors, such as the inclusion of patients with bipolar disorder, may influence the nature of this association [30]. Hence, this characteristic has significant importance when evaluating this group, since it directly impacts the therapy and prognosis. Another intriguing discovery is that the genetic variables influencing the likelihood of developing alcohol dependency seem to be mostly separate from those involved in the frequency of alcohol usage. Alcohol use disorders are genetically linked to major depressive disorder (MDD), specifically MDD with typical neurovegetative symptoms. On the other hand, the genetics of alcohol consumption are negatively associated with atypical neurovegetative symptoms and cardio-metabolic disorders. This suggests that patients with atypical depressive symptoms may have broader metabolic abnormalities.

Step 2: Genotyping for Cytochrome P450

If the first treatment option, determined by the specific symptom profile, medication tolerance, and other clinical criteria, does not provide the desired results or is not well tolerated, medical professionals should take into account the genotyping of variations in the CYP2D6 and CYP2C19 genes (Figure 1). The metabolism of most antidepressants is mostly carried out by two CYP450 isoenzymes. These isoenzymes have highly variable genes, meaning they have several known genetic variations that might affect the transcription and activity of the encoded enzyme [32]. The classification of individuals based on the type and quantity of variations in genes responsible for CYP450 enzymes can be divided into four main metabolizing groups: extensive metabolizers (EMs) who have no genetic variants that affect enzyme function, poor metabolizers (PMs) who carry two inactive alleles, intermediate metabolizers (IMs) who have either one inactive allele or two partially active alleles, and ultrarapid metabolizers (UMs) who typically have gene duplications [33].

Studies have shown a connection between a person's genetic makeup and the levels of drugs and their byproducts in their blood. Based on this information, dosage adjustments were determined for individuals classified as poor metabolizers (PMs) and ultra-rapid metabolizers (UMs). Additionally, there are specific recommendations for drug selection and dosage for over 10 antidepressants, with varying levels of recommendation [32]. In general, it is recommended to choose an antidepressant medication that is not broken down by a faulty CYP450 enzyme (known as PMs or IMs) or by a CYP450 enzyme that is too active (known as UMs). This is done to prevent serious side effects or ineffective therapy, as advised by recommendations [32]. Alternatively, the dosage of the medicine should be modified and careful monitoring should be

implemented, including the use of therapeutic drug monitoring (TDM) if it is available.

The guideline compiled by the Clinical Pharmacogenetics Implementation Consortium [32] provides solid evidence supporting the use of amitriptyline, nortriptyline, and paroxetine, which are TCAs and an SSRI respectively. For citalopram and escitalopram, which are mainly broken down by CYP2C19, the level of recommendation is moderate. This is because there is evidence that the risk of side effects is moderately higher in individuals with CYP2C19 poor metabolizer status who are treated with standard doses. These side effects include sexual side effects. However, it is also observed that symptom improvement and symptom remission are better in poor metabolizers compared to extensive metabolizers [34]. When it comes to antidepressants like citalopram and escitalopram that are linked to the risk of QTc prolongation, it is advisable to change the dosage for patients with poor metabolizer status. Additionally, doing a baseline electrocardiogram (ECG) and evaluating any existing heart-related conditions is a wise approach.

In summary, if there is no compelling evidence opposing the selection of a specific antidepressant based on the individual's metabolizing status for CYP2D6/CYP2C19 and the clinical history/symptom profile supports the use of that drug, it is a reasonable choice to proceed and modify the drug dosage according to guidelines, inform the patient about potential risks, increase clinical monitoring, and utilize therapeutic drug monitoring (TDM) if it is accessible.

Although the existing data indicates that patients who did not react well or tolerate at least one prior treatment are the group that is most likely to get benefits from CYP2D6/CYP2C19 genotyping [10,36], there is still no conclusive proof, and various suggestions may be found. According to the French National Network of Pharmacogenetics, it is recommended to do CYP2D6/CYP2C19 genotyping before starting antidepressant treatment, particularly in individuals who are at a high risk of experiencing harmful side effects [37].

Genotyping for CYP2D6/CYP2C19 is not widely offered in clinical services and is often not covered by national health care systems. Consequently, if a patient is prepared to pay for their own genetic testing, they might consider using commercial pharmacogenetic tests. Based on a recent analysis of tests available in Canada, the median cost of these tests is CAD 499, with a range of CAD 199 to CAD 2,310. It should be noted that pricing may vary in different countries [38]. When considering this possibility, clinicians should be aware that commercial pharmacogenetic tests often include genetic variants that are not recommended by guidelines [39]. To make an informed choice, two main points should be considered: the test should include all the genetic variants recommended by guidelines [32]. It is important to note that the frequency of variants in CYP2D6/CYP2C19 genes varies across different ethnicities, particularly for patients of non-European ancestry; the test report should provide sufficient detail and present the results for each gene and variant tested. This allows for consideration of the level of evidence for each variant according to guidelines when selecting the appropriate antidepressant [40].

Step 3: Potential Applications of Polygenic Risk Scores

The decreasing cost of genome-wide genotyping has led to a rapid expansion of direct-to-consumer enterprises providing genetic testing services. The pricing range is GBP 50–129 in the United Kingdom, with potential variations in other countries. They provide diverse information, often including health concerns. By early 2019, about 26 million individuals had undergone one of these tests, and the numbers are growing quickly [11]. Genome-wide arrays offer genotypes for numerous genetic variants across the entire genome. These data can be utilized to compute polygenic risk scores (PRS) for both psychiatric and non-psychiatric traits. PRS is a measure that represents the genetic burden imposed by the collective group of risk variants associated with a particular trait, such as non-response to antidepressants or the risk of a specific disease (Figure 1). Although the polygenic risk scores (PRS) for psychiatric illnesses or response to antidepressants did not demonstrate robust predictive ability, they may be useful when combined with non-genetic risk variables [26,41,42]. However, there is currently insufficient data to support this claim. However, a comprehensive understanding of the interpretation and potential therapeutic significance of PRS is crucial in clinical settings, given the rapid spread of direct-to-consumer goods.

Currently, studies have shown that polygenic risk scores (PRS) provide additional information to non-genetic risk factors for coronary artery disease (CAD), type 2 diabetes (T2D), breast and prostate cancers, and Alzheimer's disease [43]. This is particularly important in the context of major depressive disorder (MDD), since there is a high prevalence of comorbidity with CAD and T2D [44,45]. The addition of the CAD PRS (Polygenic Risk Score) to traditional risk factors such as blood pressure, cholesterol levels, and smoking habits has been demonstrated to enhance predictive ability. Furthermore, it aids in identifying patients who are more likely to benefit from statins, particularly those with the highest CAD PRS. Interestingly, informing patients about their genetic risk for CAD when making decisions about starting statin therapy has led to improved outcomes. Hence, the presence of CAD PRS in a patient with MDD may provide supplementary guidance for selecting treatment options. It is crucial to exercise caution when prescribing medications that are linked to a greater likelihood of cardio-metabolic side effects, particularly in individuals with a high CAD PRS. Additionally, the assessment of non-genetic risk factors for CAD should also be taken into account.

The risk of incident T2D was determined to be 3.45 times greater in the highest T2D PRS quintile compared to the lowest quintile, after accounting for body mass index and other established predictors. Incorporating PRS into other factors in a prediction model for 5-year T2D risk led to a continuous net reclassification improvement of 0.32 (95% confidence interval: 0.21–0.44) [46]. Hence, the polygenic risk scores (PRS) for type 2 diabetes (T2D) has the potential to be useful in guiding the prescription of antidepressants and monitoring patients clinically. This is similar to what we discussed regarding the PRS for coronary artery disease (CAD). However, there is currently no evidence regarding the specific threshold of the PRS that should serve as a warning against prescribing medications associated with the risk of cardio-metabolic side effects.

The available information regarding the potential usefulness of PRS in predicting the response to antidepressant treatment is lacking [26,47]. The first findings provide evidence that the odds ratio (OR) for non-response is 2.23 (with a 95% confidence range of 1.21–4.10) in the highest percentile of schizophrenia PRS compared to the lowest quintile [26]. A research conducted on a larger sample size yielded similar findings [6]. The study demonstrated that individuals with a greater genetic predisposition for schizophrenia are more likely to have a less favorable response to lithium treatment in bipolar disorder. This discovery expands upon prior research that focused only on major depressive disorder (MDD). Another initial discovery indicates that patients diagnosed with Major Depressive Disorder (MDD) who have a low level of schizophrenia Polygenic Risk Score (PRS) may have a more positive response to treatment with antidepressant medication alone, as opposed to combining antidepressants with atypical antipsychotics. Conversely, patients with a high level of schizophrenia PRS had a poor response to both treatment approaches [26].

Discussion

The treatment of Major Depressive Disorder (MDD) now relies heavily on a trial and error method or individualized approaches, which may lead to unsatisfactory outcomes and often fail to provide complete symptom relief. This can result in ongoing functional impairment and an increased likelihood of relapse or recurrence. This review presents a systematic approach to assist clinicians in determining the criteria and actions to consider when prescribing treatments for patients with Major Depressive Disorder (MDD). It focuses on cases where Selective Serotonin Reuptake Inhibitors (SSRIs) may be less effective and where other medical conditions are contributing to the development of the disease (Figure 1). The proposed steps are arranged in a hierarchical manner. The initial step serves as the foundation of the process and involves the crucial evaluation that should be conducted in all patients. This evaluation entails the clinical assessment of the individual symptom profile, which can be compared with the pharmacological properties of the medications that are currently available [5].

Additionally, it should be interpreted in consideration of the genetic diversity of depressive symptoms. The significance of this last point lies in the fact that different types of depressive symptoms are associated with partially overlapping genetic factors. For instance, the genetic correlation between depression characterized by atypical symptoms and depression characterized by typical neurovegetative symptoms is 0.54 (standard error = 0.14), where a genetic correlation of one indicates complete genetic overlap. Furthermore, these subtypes of Major Depressive Disorder (MDD) share genetic similarities with distinct traits, which may have implications for treatment. Genetic research has shown that the genetic variations that influence the likelihood of Major Depressive Disorder (MDD) are shared to different degrees with other psychiatric and non-psychiatric features.

In this study, we have explored that MDD consists of subtypes that are clinically and genetically diverse. If the initial step of the suggested procedure fails and the patient still experiences depression despite receiving appropriate treatment in terms of duration and dosage, or if the patient experiences intolerable side effects,

medical professionals should contemplate genotyping for CYP2C19/CYP2D6 variants. This may provide further information to aid subsequent prescription choices, since people with modified drug metabolism may have a more favorable response or tolerance to certain antidepressants compared to others. If the use of prescribing recommendations based on CYP2C19/CYP2D6 genotyping does not improve the ability to identify an effective and well-tolerated treatment, there are no other criteria supported by evidence that can guide the selection of specific medications for MDD. However, there are several options available with varying levels of evidence for their effectiveness in treating TRD [12].

As step 3, we proposed assessing the potential clinical significance of PRS, if applicable (i.e., if the patient chooses to do direct-to-consumer genetic testing and is prepared to disclose the findings to their healthcare provider). Currently, PRS have limited therapeutic uses and are mostly used in psychiatry. However, they may be useful in identifying people who are at risk of developing cardio-metabolic problems and can assist avoid drugs that may have these adverse effects in this particular set of patients. Genomic medicine is now undergoing fast transformation, which means that the prediction accuracy of PRS (Polygenic Risk Scores) and their clinical uses may alter quickly in the near future. There are web tools available that can help you stay informed about the latest information in this area. One such tool is the Polygenic Score (PGS) Catalog, which contains information on more than 200 PRS (Polygenic Risk Score) for 100 different traits, including MDD (Major Depressive Disorder) and schizophrenia.

The catalog also provides details about PRS metrics, such as the AUC (Area Under the Receiver Operating Characteristic Curve), which estimates the percentage of individuals correctly identified as cases by the PRS. Although a PRS for antidepressant response is not yet available due to the limited power of previous samples [47], recent findings from a larger sample size indicate that the PRS is a significant predictor of symptom improvement and remission in response to antidepressant treatment, although the amount of variance explained is still quite low [6]. Impute.me is a web tool that helps individuals understands their genome-wide genotyping data. It offers current information on the impact of individual genetic variants and polygenic risk scores (PRS) for various traits, such as psychiatric disorders and the response to clozapine in schizophrenia [51].

Conclusion

Users have the option to upload their genome-wide data and determine their polygenic risk scores (PRS) for various characteristics. They may also find out how their PRS value compares to a reference group. A fundamental understanding of these resources and their utilization will become increasingly pertinent in clinical practice, given the exponential rise in individuals undergoing at-home DNA tests. It is advisable for treating physicians to provide guidance on result interpretation to prevent unwarranted distress, superfluous clinical testing, or unnecessary treatments. The decreasing costs of genotyping and DNA sequencing will make it easier for national health care systems to offer these services. Initially, they will be provided to individuals with rare and severe disorders, and eventually, they may be extended to a larger portion of the population, including healthy

individuals. This is because effective preventive strategies for most diseases may become accessible.

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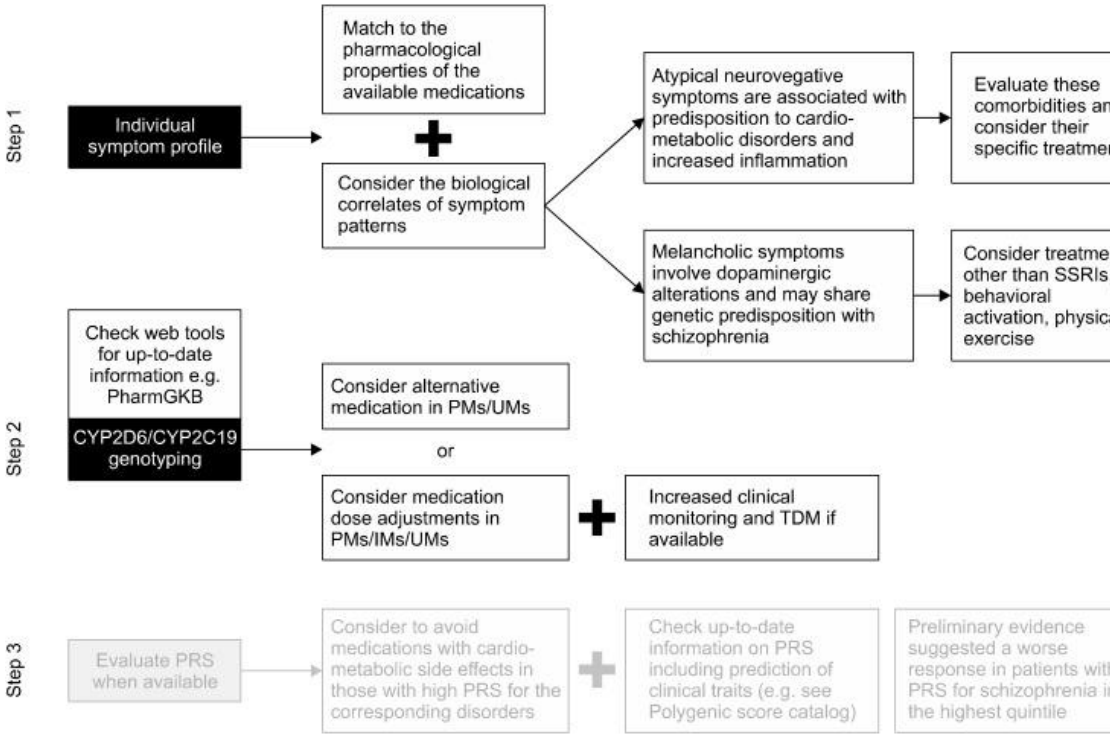

Figure 1. Proposed methodology for tailoring therapy in depression