Pharmacogenetic-guided treatment in major depressive disorder

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Abstract. Depression affects millions of individuals worldwide, presenting a significant challenge for clinicians striving to match patients with effective treatments. Conventional antidepressant therapy involves a trial-and-error approach, leading to delayed relief, increased healthcare costs and patient distress. Recent advancements in pharmacogenetics provide a promising avenue for personalized treatment, leveraging genetic information to optimize medication selection and dosage adjustments. The present study aimed to investigate the extent of genetic polymorphisms that affect antidepressant drug metabolism and efficacy in a psychiatric population. Additionally, the present study investigated pharmacogenetic-guided treatment outcomes in a sub-population of patients diagnosed with major depressive disorder. Pharmacogenetic-guided therapy represents a novel strategy which can be used to personalize depression treatment, providing the potential to enhance efficacy, safety and patient satisfaction. While challenges persist, accumulating evidence supports its integration into routine clinical practice, heralding a new era of precision medicine in mental health care.

Introduction

Although effective pharmacologic therapies for mental illnesses are available, their efficacy is restricted, largely due to the underlying genetic variability across psychiatric patients and the subsequent low compliance due to the frequency of side-effects (1). Specifically, as regards depression, one third of patients receiving antidepressant medications do respond to treatment and two thirds of patients do not achieve remission (2). Additionally, ~42% of patients discontinue their prescribed antidepressant medication in the 1st month and 70% of patients discontinue during the first 3 months of treatment, while 45% of patients do not take their medication as indicated by their doctor (3,4).

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The current standard of care in psychiatric practice relies on a trial-and-error approach that combines the experience of a physician with specific clinical indicators. For patients sharing the same diagnosis, most commonly, the same medication is prescribed, usually at the recommended dose as per the drug label. Due to interindividual differences with regards to genetics and lifestyle, this process can take weeks, months, or even years before the right medication is found. Pharmacogenetic (PGx) testing, however, can personalize treatment and dosage selection, and may thus help to avoid these long periods of trial-and-error, empowering a precision medicine approach in mental health care (Fig. 1). PGx testing can identify, at a personalized level, genetic characteristics that may predict the clinical response of a patient to a certain medication and the probability of adverse events being developed, based on specific genetic variants that they carry, which, among other things, can alter the activity of enzymes that metabolize central nervous system (CNS) medications, such as antidepressants (5,6).

Antidepressant medications are mainly metabolized by cytochrome P450 (CYP450) enzymes, including CYP2D6 and CYP2C19 (1). Genetic variants, specifically single nucleotide polymorphisms (SNPs), in these genes can alter the activity levels of these enzymes, resulting in a reduced or no activity, or even increased or significantly increased activity. The resulting predicted phenotypes are defined as poor, intermediate, rapid and ultra-rapid metabolizer, respectively. Psychiatric patients with the poor or intermediate metabolizer phenotypes may be at an increased risk of developing adverse events when treated with medications metabolized by these enzymes, due to the slower degradation of the drugs that results in higher concentrations in the plasma for prolonged periods of time. These patients, once identified by PGx testing, would be recommended to initiate therapy on a lower dose, slow titration, or even alternative medication. Patients with a rapid or ultra-rapid metabolizer genotype, on the other hand, could experience either side-effects or treatment ineffectiveness as a result of the drugs being metabolized too rapidly and failing to act in time (7). These patients, once identified by PGx testing, would be recommended fast titration, initiate therapy on a higher dose, or even alternative medication not metabolized as rapidly.

The most recent meta-analyses on major depressive disorder (MDD) indicate that PGx-guided treatment for moderate-to-severe depression is significantly more likely to result in response and remission than treatment as usual (TAU) (8,9). Despite the low confidence about the extent, due

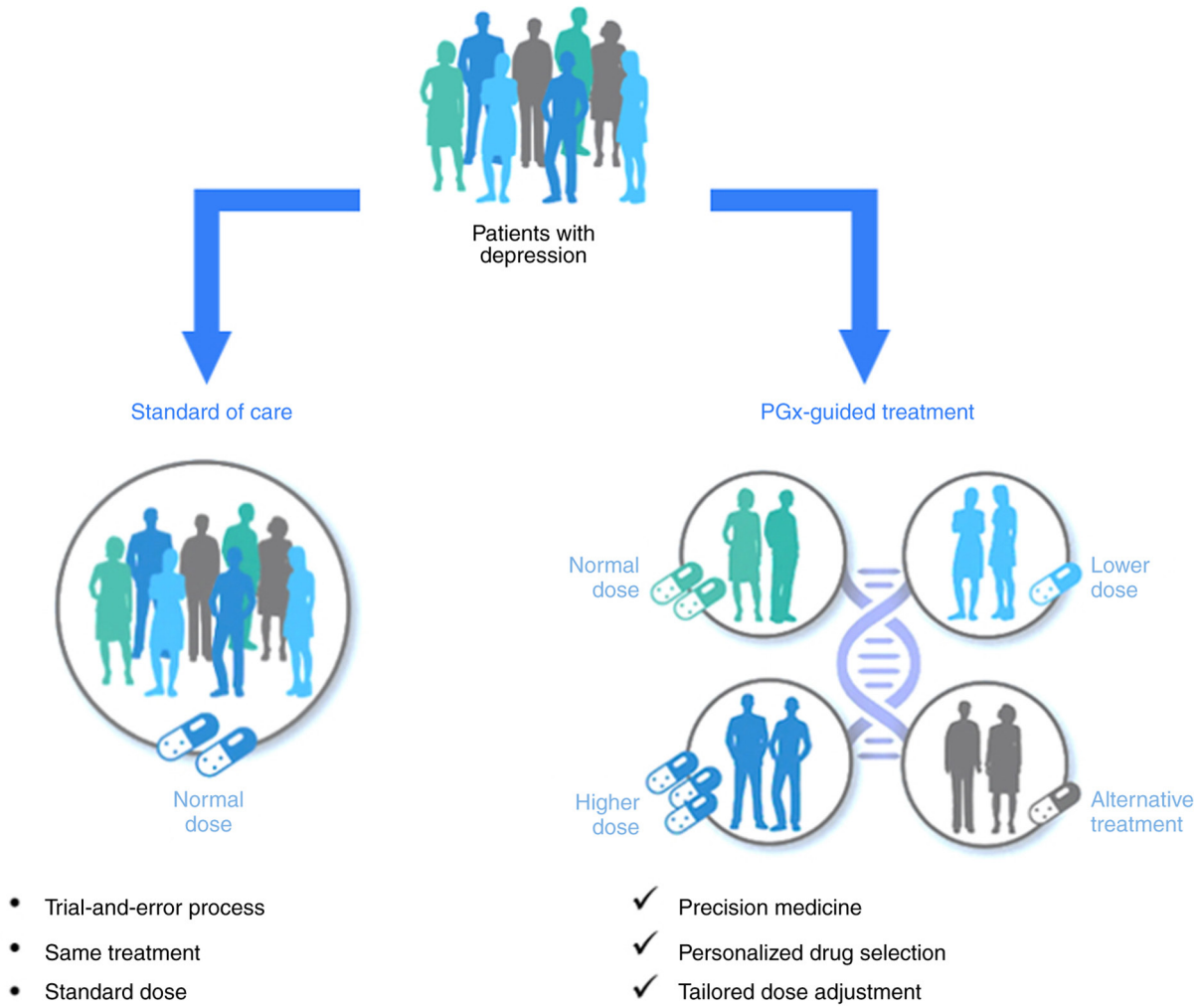

Figure 1. Comparison of the standard of care and pharmacogenetic-guided approach for the treatment of patients with depression. PGx, pharmacogenetic.

to study limitations, there is confidence in the direction. More precisely, the positive effects of PGx guidance for individuals suffering from moderate-to-severe MDD may have significant benefits for both the patients and the healthcare system, due to the scope and magnitude of the disorder and its consequences (8,9).

The present study aimed to examine the extent of genetic variants in a psychiatric population, with regards to genes implicated in antidepressant drugs metabolism, comprising CYP2D6 and CYP2C19, and response, including FKBP prolyl isomerase 5 (FKBP5). FKBP5 is a gene that encodes a protein involved in the regulation of the stress response and has been implicated in the pathophysiology of MDD. Variants in FKBP5 have been shown to influence the efficacy of antidepressant treatments, thus rendering it a key factor in pharmacogenetic studies. Specifically, the SNP rs4713916 in FKBP5 has been shown to be associated with varying responses to antidepressant medications, categorizing individuals into groups with a good, increased or reduced response to treatment (10,11). Furthermore, the present study employed a questionnaire to assess the clinical utility of an *in vitro* diagnostic PGx test, the iDNA PGx CNS (12,13), in a population of patients suffering from MDD. Specifically, patient responses were collected, following PGx testing and personalized drug and dosage selection, in terms of response to treatment, severe adverse events, changes in medication, and frequency of doctor visits and communications.

Materials and methods

Patient data and analyses. Of note, the present study used pre-existing anonymized data that does not allow for the identification of individuals. The present study did not involve any invasive procedures or direct interaction with patients. The present study only utilized pre-existing anonymized genetic data. These factors place the research outside the scope of requiring formal ethical review, as it poses no foreseeable risks to individuals. Nevertheless, it was ensured that the study adhered to the highest ethical standards available and was carried out in accordance with the Declaration of Helsinki. All participants were able to and provided informed consent, allowing for the use of their anonymized genetic data for research and statistical purposes. This also applies to the questionnaire survey for which all participants were capable of and provided informed consent, allowing for the use of their answers for research and statistical purposes. Moreover, all participants had the right to withdraw their data at any time, ensuring their autonomy and control over their information.

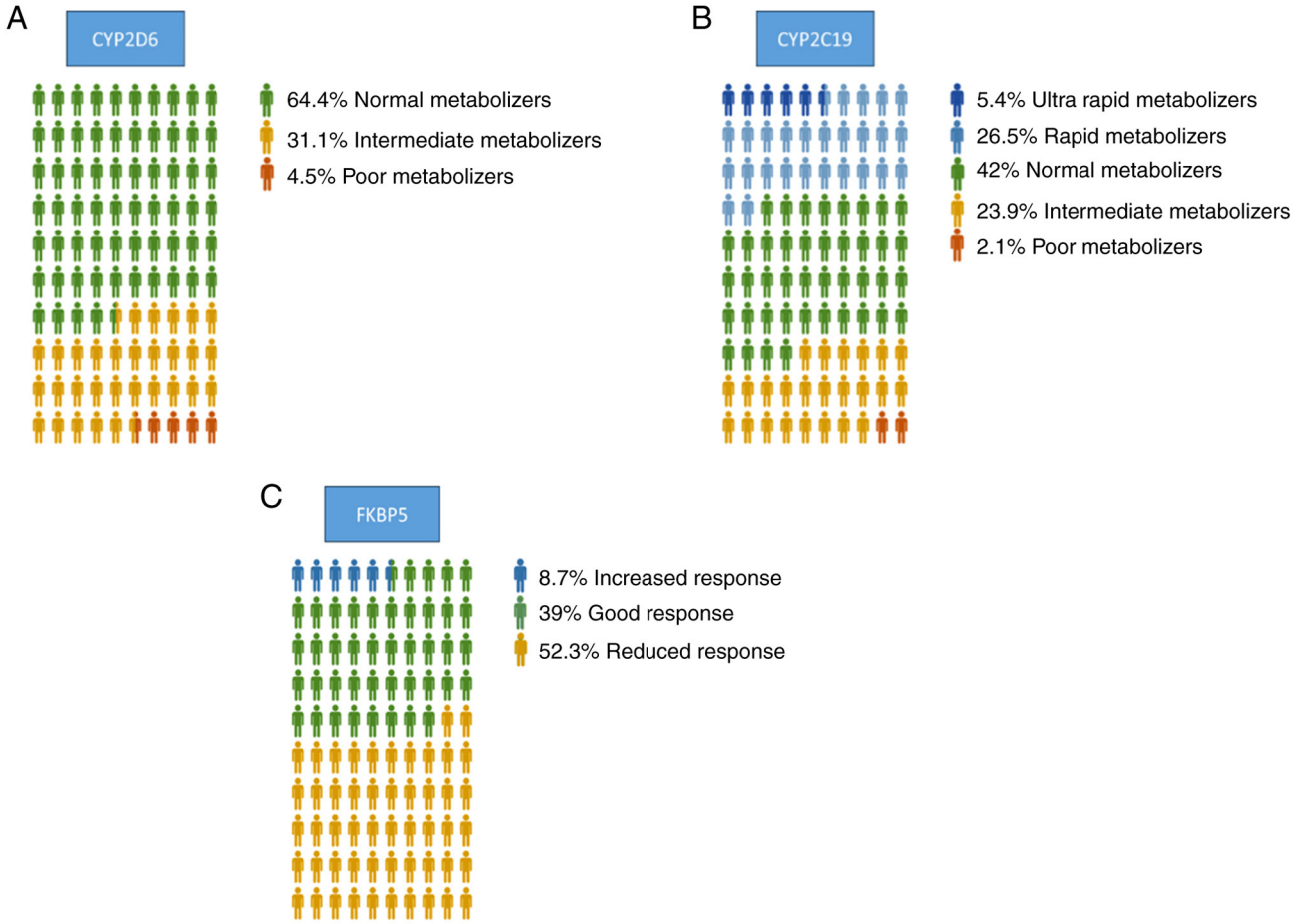

Figure 2. Distribution of (A) CYP2D6 and (B) CYP2C19 metabolizer status genotypes, and (C) FKBP5 rs4713916 genotypes in the psychiatric population (n=1,387). CYP, cytochrome P450; FKBP5, FKBP prolyl isomerase 5.

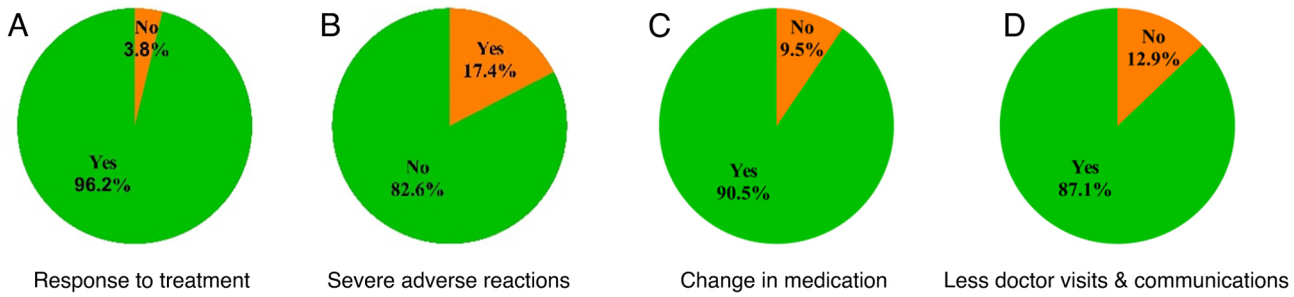

Figure 3. Outcomes of patients suffering from major depressive disorder (n=132) following pharmacogenetic-guided treatment. (A) Response to treatment. (B) Severe adverse reactions. (C) Change in medication. (D) Fewer doctor visits and communication. For statistical analysis, a Chi-squared test was employed and the results are presented in Table I.

The distribution of CYP2D6, CYP2C19 and FKBP5 genotypes was analyzed in a psychiatric patient population of 1,387 individuals in Greece. The genetic material of patients was collected from buccal swab samples using the iDNA PGx CNS kit. A minimum DNA concentration of 50 ng in 1 ml sterile water was required to ensure sufficient DNA yield for genotyping. DNA extraction and purification were performed employing the PureLink genomic DNA mini kit and genotyping was performed using PCR on custom made iDNA PGx CNS OpenArrays on a QuantStudio 12K Flex Real-Time PCR (Thermo Fisher Scientific, Inc.). A bioinformatics platform, including an internal iDNA PGx CNS database and an interface, was employed for reporting the genotypes and PGx-based recommendations. Specifically, the iDNA PGx CNS panel, evaluates 24 SNPs across 13 genes (CYP2C19, CYP2C9, CYP2D6, DRD2, DRD3, EPHX1, FKBP5, GRIK1, MC4R, SCN1A, ANKK1/DRD2, HTR2C and UGT2B7) and their interactions with 30 CNS drugs, comprising antidepressants (amitriptyline, citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine and vortioxetine), antipsychotics (amisulpride, aripiprazole, clozapine, haloperidol, olanzapine,

Table I. Outcomes in patients suffering from major depressive disorder (n=132) following pharmacogenetic-guided treatment.

	Response to treatment	Severe adverse reactions	Change in medication	Fewer doctor visits and communications
Yes, n (%)	127 (96.2)	23 (17.4)	119 (90.5)	115 (87.1)
No, n (%)	5 (3.8)	109 (82.6)	13 (9.5)	17 (12.9)
P-value	<0.01	<0.01	<0.01	<0.01

paliperidone, quetiapine, risperidone and ziprasidone), antiepileptics (carbamazepine, lamotrigine, phenytoin, topiramate and valproic acid) and others (clobazam, diazepam, donepezil and galantamine). The findings concerning the total 24 SNPs of the panel across the aforementioned 13 genes have been previously published (12).

Following genotyping analysis, patients were categorized into a series of different predicted metabolizer status phenotypes, including normal, intermediate, and poor metabolizers, based on their CYPD2D6 and CYP2C19 genotypes, as well as rapid and ultra-rapid metabolizers for CYP2C19. Patients were also categorized based on their predicted phenotype with regards to response to antidepressant medications, specifically into three categories, comprising good, reduced, and increased response, according to their FKBP5 SNP rs4713916 genotype.

A summary of the genetic analysis in steps is presented as follows: i) DNA extraction and purification from buccal swab samples were performed using the PureLink genomic DNA mini kit; ii) genotyping with PCR was performed using custom made iDNA PGx CNS OpenArrays on QuantStudio 12K Flex Real-Time PCR; iii) bioinformatics analysis assigning genotypes to metabolizer and response predicted phenotypes.

Finally, a sub-population of 132 patients diagnosed with MDD was requested to answer a short questionnaire on the following topics: i) Treatment response; ii) severe adverse events; iii) treatment modifications; and iv) patient-physician interactions.

Statistical analysis. Data are presented as number and percentage and statistical analysis was performed using IBM SPSS (version 30; IBM Corp.) and Minitab (version 22) (https://www.minitab.com/en-us/products/minitab/) statistical software. Statistical significance was calculated using the Chi-squared test. A value of $P<0.05$ was considered to indicate a statistically significant difference.

Results

Regarding CYP2D6, 64.4% of the patients were identified as normal metabolizers, 31.1% of the patients were identified as intermediate metabolizers, and 4.5% of the patients were identified as poor metabolizers (Fig. 2A). For CYP2C19, 42% of the population exhibited normal metabolizer status, while 5.4% were ultra-rapid metabolizers, 26.5% were rapid metabolizers, 23.9% were intermediate metabolizers and 2.1% were poor metabolizers (Fig. 2B). The analysis of the genetic distribution in SNP rs4713916, in FKBP5, revealed that 39% of the subjects were expected to exhibit a good response, 8.7% an increased response, while 52.3% were identified to carry a reduced response genotype (Fig. 2C).

In patients diagnosed with MDD that followed personalized drug and dosage selection by their doctor through PGx guidance, significant improvements in symptoms were noted by 96.2% ($P<0.01$) of individuals (Fig. 3A and Table I). Furthermore, 82.6% ($P<0.01$) did not report severe adverse events (Fig. 3B and Table I). In 90.5% ($P<0.001$) of patients, treatment modifications were made, including dosage adjustments or selection of an alternative medication (Fig. 3C and Table I). Finally, 87.1% ($P<0.01$) of patients reported a reduction in visits and communications with their doctors following pharmacogenetically guided treatment (Fig. 3D and Table I).

Discussion

Depression, a prevalent and debilitating mental health disorder, affects millions of individuals worldwide, presenting a significant challenge for clinicians striving to find effective treatments for their patients (2). To date, therapy is based on a trial-and-error approach, leading to delayed relief, increased healthcare costs, and patient hardship (6). However, recent advancements in PGx-guided therapy offer a promising avenue for personalized treatment, leveraging genetics to improve medication selection and dosage adjustments.

The efficacy and tolerability of antidepressants vary widely among individuals, partly due to genetic differences influencing drug metabolism and other molecular mechanisms. PGx studies have identified several key genes implicated in antidepressant response, including those encoding cytochrome P450 enzymes (1,14). By analyzing genetic variants relevant to drug metabolism and pharmacodynamics, clinicians can tailor treatment strategies to match genetic profiles of patients, potentially improving outcomes and minimizing adverse effects (5).

A growing body of evidence supports the utility of PGx testing in guiding antidepressant therapy (15-19). Studies have demonstrated that individuals receiving PGx-guided treatment experience higher response rates, a more rapid improvement of symptoms and fewer adverse events compared to those managed conventionally (8,9). A recent umbrella review and updated meta-analysis aimed to evaluate the effectiveness and safety of PGx in guiding antidepressant prescribing for patients with depression (20). Patients receiving PGx-guided therapy had a significantly higher likelihood of achieving remission, with rates ranging from 41 to 78%. The response rate for these patients was also improved, ranging from 20 to 49%, compared to those receiving TAU (20). Although the present study

lacks a control group, the findings with regards to symptom improvement, reported by 96.2% of patients, are in the same direction. Moreover, while there is limited available evidence on the safety of PGx-guided treatment (20), the present study demonstrawted that 82.6% of patients did not report any side-effects following PGx-guided medication, indicating that PGx guidance may lead to better safety and tolerability. Furthermore, integrating PGx testing into routine clinical practice has shown feasibility and cost-effectiveness, with some healthcare systems adopting it as standard care (21-23). The real-world data presented herein suggest that PGx-guided therapy enhances treatment adherence, reduces healthcare utilization, and enhances patient satisfaction, highlighting its potential to revolutionize depression management.

Despite its promise, several challenges remain in the widespread implementation of PGx-guided therapy for depression. These include issues related to test accessibility, interpretation of results, clinician education and reimbursement. Additionally, further research is required to elucidate optimal testing protocols, refine bioinformatic algorithms and assess long-term health outcomes. Collaborative efforts among researchers, clinicians, policymakers and industry stakeholders are crucial to address these challenges and maximize the clinical utility of pharmacogenetics.

PGx-guided therapy represents a groundbreaking approach to individualizing depression treatment, offering the potential to enhance efficacy, safety, and patient satisfaction. While challenges persist, accumulating evidence supports its integration into routine clinical practice, heralding a new era of precision medicine in mental health care. By leveraging genetic insights, clinicians can empower patients with personalized treatment plans, ultimately improving outcomes and quality of life for those living with depression.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NP conceptualized the study. NP, AS and TF analyzed the data. EN and ES performed laboratory analysis, DNA isolation and genotyping. NP and AS wrote the manuscript. All authors confirm the authenticity of all the raw data. All authors reviewed and edited the manuscript, and all authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study used pre-existing anonymized data that does not allow for the identification of individuals. The present study did not involve any invasive procedures or direct interaction with patients. The present study only utilized pre-existing anonymized genetic data. These factors place the research outside the scope of requiring formal ethical review, as it poses no foreseeable risks to individuals. Nevertheless, it was ensured that the study adhered to the highest ethical standards available and was carried out in accordance with the Declaration of Helsinki. All participants were able to provided informed consent, allowing for the use of their anonymized genetic data for research and statistical purposes. This also applies to the questionnaire survey for which all participants were capable of and provided informed consent, allowing for the use of their answers for research and statistical purposes. Moreover, all participants had the right to withdraw their data at any time, ensuring their autonomy and control over their information.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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