

An Effective Method to Facilitate Personalized and Precise Medicine for Schizophrenia Treatment Based on Pharmacogenomics

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ABSTRACT

Background: Schizophrenia is a serious mental illness affecting 0.3-0.7% of the world's population. It is a classic quantitative genetic disease and is affected by a variety of common and rare genetic variants.

Methods: To facilitate personalized and precise medicine for schizophrenia treatment, we designed a program by genotyping a panel of related genes for schizophrenic patients using MassARRAY time-of-flight mass spectrometry. The program was tested in an observational clinical study conducted at the Hulunbuir Mental Health Center of China. In the study, a total of 254 patients diagnosed with schizophrenia were recruited and genotyped. The genotyping results were used to generate reports listing where the 16 included antipsychotics should be placed: "Use as directed," "Use with caution," or "Use with caution and with frequent blood concentration monitoring" categories. Seventy-two of the patients completed the 24-week follow-up observation, during which their PANSS scores were assessed at eight time points.

Results: For all of the subjects who completed the study, the PANSS scores dropped significantly, showing the effectiveness of the treatment. During the 24-week study, PANSS scores of patients whose medications were consistent ($N = 48$) with their genetic test results dropped from 84.3 (SD = 12.4) to 58.8 (SD = 15.3), and average PANSS change rate reached 56.1% after 24 weeks. In contrast, PANSS scores of patients with genetic tests reported as "Use with caution" or "Use with caution and with frequent blood concentration monitoring" ($N = 24$) dropped from 81.1 (SD = 10.5) to 63.8 (SD = 10.1), and their average PANSS change rate was 37.6%.

Conclusions: This research indicates that our pharmacogenomic-based program could be a suitable and effective tool to facilitate precise medication in schizophrenia treatment.

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INTRODUCTION

Schizophrenia is a serious, chronic, and persistent mental illness with a global incidence of about 0.3-0.7%.¹ The disease mostly occurs in late adolescence or early adulthood and shows varying degrees of social or occupational functional impairment. Research has demonstrated that the causes of schizophrenia include genetic factors.² There is evidence implying that 70-80% of the individual differences in risk to schizophrenia are associated with genetics.³ The current treatment of schizophrenia, however, has not yet taken the genetic variation sufficiently into account.

The essence of clinical drug treatment is basically a process of effective drug use. Both the physical conditions of the patients (age, gender, physiology, pathology, genetics) and the drugs administered (dose, dosage form, administration time, dosing interval, combination medication) could be

the master factors affecting the final therapeutic effect of drugs.⁴ More and more studies demonstrate that genetic factors may play the most important role in affecting the differential response to drugs. Pharmacogenomics studies the role of the genome in drug response and analyzes how the genetic makeup of an individual affects his/her response to drugs by correlating genetic variation and gene expression level with pharmacokinetics (drug absorption, distribution, metabolism, and elimination) and pharmacodynamics (effects mediated through a drug's biological targets). The application of pharmacogenomics and big data analysis in psychiatric research will provide patients with mental disorders an important drug therapy for individualized medication and reduce the incidence of adverse reactions, thus promoting the advancement of precision medicine.⁵⁻⁷

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Major depressive disorder (MDD) is another complex psychiatric disease with millions of sufferers around the world. There has been considerable reported research on how genetic polymorphisms may impact patients' reactions to anti-depression drugs, including ones carried out in Turkey.^{8,9} In the past decades, several algorithms have been developed to guide the medication based on patients' genetic test results, for example, GeneSight¹⁰⁻¹⁷ and IMPACT (Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment).¹⁸ GeneSight tests the genetic polymorphisms of several selected genes, mostly related to MDD drug metabolism, efficacy, or adverse drug reactions (ADRs). In the large-scale clinical trial published in 2019,¹⁶ 1167 MDD patients were randomly assigned into two groups: the treatment of one group was conducted under the guidance of GeneSight recommendations based on genetic test results, the other followed the traditional non-guided treatment protocol. Each patient was evaluated regularly using the 17-item Hamilton Depression Scale (HAMD-17) to assess how serious his/her depression was during the trial period. After 8-week observation, the response rate (defined as the HAMD-17 score having dropped more than 50%) in the guided group was 30% higher than that in the non-guided group, while the remission rate (defined as the HAMD-17 score having dropped below 7) was 50% higher in the guided group over the non-guided group. The results demonstrate that pharmacogenomics has the potential to guide rational drug therapy to facilitate personalized and precise medicine.

To the best of our knowledge, no clinical study has been published in which a GeneSight-like program was used for guiding schizophrenia drug prescription based on a genetic test. In this paper, we describe a program we developed and the results of an observational clinical study we carried out in Hulunbuir Mental Health Center, China. Although this is not a randomized perspective study exactly like the ones performed by GeneSight, it does offer valuable information and its usefulness may be further proved by larger-scale, double-blind, multi-center trials in the near future.

METHODS

Program Design

This program is designed to assist physicians to better prescribe antipsychotics and ensure maximum efficiency with minimal adverse effects based on patients' genotypes. A total of 16 drugs are included in the package: amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, haloperidol, perphenazine, thioridazine, zuclopenthixol, sulpiride, loxapine, chlorpromazine, and perospirone. Some of them are typical antipsychotics (perphenazine, thioridazine, etc.). Some are second-generation antipsychotics (SGA), also called atypical antipsychotics, including risperidone,

quetiapine, olanzapine, ziprasidone, aripiprazole, etc. Genes were selected based on the PharmGKB database (<https://www.pharmgkb.org/>), as well as by taking FDA specifications, CPIC (the Clinical Pharmacogenetics Implementation Consortium) official guidelines, clinical study data, authoritative literature, and relevant genome databases into account. The candidate gene loci are all based on the characteristics and distribution frequency in Asians, especially Chinese people. The nucleotide polymorphisms of antipsychotic-related genes, including CYP2D6, CYP1A2, CYP3A4, DRD2, HTR1A, HTR2C, and MC4R, which affect the metabolism, efficacy, and side effects of most antipsychotics, have been detected (Supplementary Table 1).

After genotyping, each genotype for each genetic locus is assigned a weight according to an in-house algorithm (available for review upon request), based on how much this locus may impact the metabolism, efficacy, or ADR for a particular medicine. A fitness score is then calculated for each drug. If the score for a drug is above 80, it will be placed in the "Use as directed" category in our interpretive report; if the score is between 60 and 80, it is placed in the "Use with caution" category; if the score is below 60, it is placed in the "Use with caution and with frequent blood concentration monitoring" category. Thus, the physician and the tested patient may get a report like this: (Table 1). If the drug currently being used is either in the "Use with caution" or in the "Use with caution and with frequent blood concentration monitoring" categories, the physician in charge may have the option to choose another antipsychotic.

Genotyping

Epithelial *cells* were gathered by buccal swab at baseline, and the samples were then transported from the hospital to the laboratory in the Shanghai Conlight Medical Institute on the same day. Genomic DNA was extracted according to the standard phenol-chloroform procedure and analyzed using TaqMan probe-PCR and MassARRAY iPLEX platform (Agena Bioscience Inc., San Diego, CA, USA). Polymerase chain reaction (PCR) was applied to amplify the relevant genomic regions. The primers of PCR were designed using Primer Premier5 (Premier Biosoft International, Palo Alto, CA, USA) and synthesized by Sangon Biotech (Shanghai, China). Genotyping of single nucleotide polymorphisms was conducted by ABI 7500 real-time fluorescence quantitative PCR combined with TaqMan probe and arms-PCR. MassARRAY DNA based on Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry was employed to accurately identify mutation types. The *CYP2D6* alleles identified were: *1, *2, *2A, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, and CNV. The identified *CYP1A2* alleles were: *1, *1C, *1E, *1F, *1K, *3, *4, *6, *7, *8, *11, *15, and *16. The identified *CYP3A4* alleles were: *1, *20. The metabolizer statuses for

Table 1. A Sample Report

Category	Drug	Response ^a	Adverse Reaction ^b	Metabolism ^c
Use as directed	Paliperidone	+	–	
	Ziprasidone	+	–	
Use with caution	Amisulpride	–	–	
	Aripiprazole	–	–	EM
	Clozapine	–	+	
	Qlanzapine	–	+	
	Quetiapine	–	–	IM
	Risperidone	+	+	EM
	Haloperidol	–	+	EM
	Perphenazine	+	+	EM
	Zuclopenthixol		+	EM
	Sulpiride	–	+	
	Loxapine	–	+	EM
	Peroxpiron		+	EM
Use with caution and with frequent blood concentration monitoring	Thioridazine		+	UM/EM
	Chorpromazine	–	+	UM

^a+, responds well to drug; -, may not respond well to drug.

^b+: high risk of adverse reaction; -: low risk of adverse reaction.

^cEM, extensive metabolizer; UM, ultra-rapid metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

CYP2D6, *CYP1A2*, and *CYP3A4* were determined according to the same methods reported in previous research studies: subjects with more than two active alleles were classified as ultra-rapid metabolizers, while those with at least one active allele were classified as extensive metabolizers. Subjects carrying two alleles of decreased activity or compound heterozygotes for one decreased activity allele in combination with a non-functional allele were termed as intermediate metabolizers. A combination of two non-functional alleles in a homozygous variant or compound heterozygous manner was classified as a poor metabolizer phenotype.¹⁹⁻²² The identified *DRD2* alleles were single nucleotide polymorphisms: rs1079597, rs1799732, and rs1799978. Rs1414334 and rs6318 of *HTR2C*, rs10042486 of *HTR1A*, as well as the SNP rs489693 on the gene *MC4R* were also genotyped. Within 72 h of sample collection, the pharmacogenomic-based report was offered to the treating psychiatrist.

Clinical Study

To test our program, we conducted a clinical study in Hulunbuir Mental Health Center, China. The convenience sampling method was adopted to select participants. The criteria for enrolling patients are detailed as follows: (1) Chinese citizen aged 18-70 years; (2) patients who had been diagnosed with schizophrenia based on the Structured Clinical Interview of DSM-IV; (3) A score ≥ 60 on the Positive and Negative Syndrome Scale (PANSS) (and ≥ 4 on at least three positive items). PANSS is a 30-item structured scale which can be divided into the positive syndrome subscale, the negative syndrome subscale, and the general syndrome

subscale²³; (4) physically healthy with all laboratory parameters within normal limits. Patients were excluded if they met any of the following exclusion criteria: (1) diagnosis of other psychiatric disorders (such as schizoaffective disorder and delusional disorder) or cognitive disorders (such as dementia and amnesia); (2) severe, unstable physical diseases (such as diabetes, thyroid diseases, hypertension, and cardiac diseases); (3) history of drug-induced neuroleptic malignant syndrome; (4) requiring long-acting injectable medication to maintain treatment adherence; (5) treated with electroconvulsive therapy during the last month; (6) previous attempted suicide, previous symptoms of severe excitement and agitation; (7) pregnant or breastfeeding; (8) contraindication to any of the drugs included in this study. The pharmacogenomic testing was offered free of charge to the study participants and any of them could opt out at any time. This study was approved by the Medical Ethics Committee of Hulunbuir Mental Health Center (approval number: 2018-051, date: December 31, 2018) and all subjects (as well as their legal guardians) provided written informed consent in accordance with the Helsinki declaration.

Two hundred fifty-four patients were initially enrolled. We genotyped a panel of related genomic polymorphisms using MassARRAY time-of-flight mass spectrometry, and test reports were generated as described in the “Program Design” section. While in general cases, the treating physicians might decide to change medication based on the test report, the medication would not change in this observational study unless there were serious adverse reactions. If medication had to be changed, the patient

would be removed from further observation. The patients were observed at 8 time points: baseline (Week 0, before treatment and genetic test), Week 2 (two weeks after genetic test, same below), Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24. At each time point, their PANSS scores were assessed based on structured clinical interviews (SCI-PANSS). All interviewers were trained before the start of this study and reached a qualified consistency (intra-class correlation coefficients higher than 0.75). Among the cohort of 254 subjects initially enrolled, 71 were removed due to lack of essential information (whether they had other physical diseases, etc.); 31 patients dropped out (or were removed) during various stages; and 152 completed the 24-week observation. Two more were later removed because they were under 18 years of age. For the remaining 150 enrolled patients, we focused on those who were prescribed with single second-generation antipsychotics including olanzapine, quetiapine, aripiprazole and clozapine. Fifty-eight patients who were either prescribed with other drugs or combinatorial medication were removed. Another 20 patients were removed because they belonged to an ethnic minority (see “Discussion” section), and 72 ethnic Han Chinese remained in the final study. Among them, 48 (66.7%) were in the “Use as directed” group, and the others (24, 33.3%) were either in the “Use with caution” or the “Use with caution and with frequent blood concentration monitoring” groups (Figure 1).

Measurements and Statistics

Demographic characteristics (such as age and gender) and disease-related characteristics (such as severity of illness assessed by PANSS, DOI (duration of illness, months), and medication history) were recorded.

Descriptive statistics were used to summarize the demographic and clinical characteristics. Nominal

variables were shown as counts (percentage) and continuous variables were shown as mean (standard error). We used the two-sided Fisher’s exact test to identify the relationship between study groups (consistent group and inconsistent group) and metabolic phenotypes or genotypes. The two-tailed independent *t*-test was used to determine difference in PANSS scores or PANSS change rates between the consistent group and the inconsistent group. We also categorized participants into two subgroups based on PANSS drop percentage with a cutoff value of 25%, 50%, or 75%. Two-sided Fisher’s exact test was used to examine the association between the study group (consistent group and inconsistent group) and the PANSS drop percentage. All analyses were performed using R (version 3.5.1). A value of $P < .05$ was considered statistically significant.

RESULTS

Demographic and Clinical Variables

Out of the cohort of 72 subjects who completed the final study, 48 of them received genetic test reports consistent with their treatment, while the reports of another 24 were inconsistent. The “consistent” group comprised 43 males (89.6%) and 5 females (10.4%), while the “inconsistent” group comprised 18 males (75.0%) and 6 females (25.0%). The average age of the 72 cohorts was 43.7 (41.4 for the “consistent” group and 48.3 for the “inconsistent” group). Other baseline information is listed in Table 2.

The Drug Metabolizing Enzyme Genotypes

The genotypes of CYP2D6, CYP1A2, and CYP3A4 were obtained. We also identified the metabolic capacity (ultra-rapid, extensive, intermediate, or poor metabolizers) for each cohort based on the activities of enzymes encoded by the above three genes (Supplementary Table 2).

For the subjects in the “consistent” group, their CYP2D6 metabolic capacity phenotypes were 62.5% extensive metabolizers, 35.4% intermediate metabolizers, and 2.1% poor metabolizers. Their CYP1A2 metabolic capacity phenotypes were 62.5% extensive metabolizers and 37.5% ultra-rapid metabolizers. Their CYP3A4 metabolic capacity phenotypes were 100% extensive metabolizers.

For the subjects in the “inconsistent” group, their CYP2D6 metabolic capacity phenotypes were 50.0% extensive metabolizers, 45.8% intermediate metabolizers, and 4.2% poor metabolizers. Their CYP1A2 metabolic capacity phenotypes were 50.0% ultra-rapid metabolizers, 45.8% extensive metabolizers, and 4.2% intermediate metabolizers. Their CYP3A4 metabolic capacity phenotypes were 91.7% extensive metabolizers and 8.3% intermediate metabolizers.

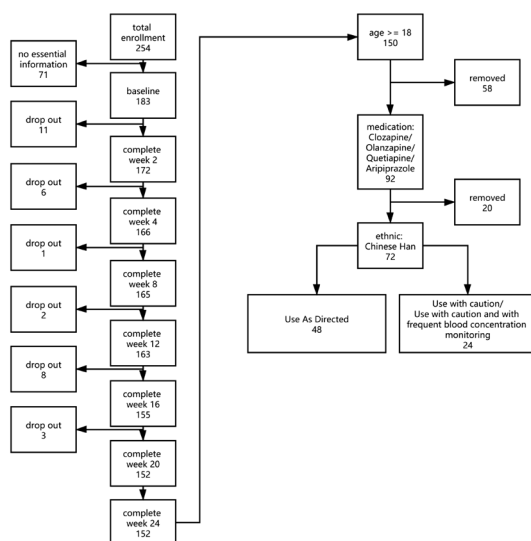


Figure 1. Chart of Study Profile.

Table 2. Demographic and Clinical Characteristics

Baseline Characteristic	Total	Clozapine	Olanzapine	Quetiapine	Aripiprazole
N (%)	72 (100)	47 (65.3)	7 (9.7)	13 (18.1)	5 (6.9)
Age (M ± SD)	43.7 ± 11.6	42.7 ± 10.2	49.4 ± 16.3	47.7 ± 11.8	34.4 ± 12.5
Gender					
Male (%)	61 (84.7)	42 (68.9)	6 (9.8)	11 (18.0)	2 (3.3)
Female (%)	11 (15.3)	5 (45.5)	1 (9.1)	2 (18.2)	3 (27.3)
PANSS baseline	83.2 ± 11.8	83.2 ± 11.9	79.0 ± 11.4	85.8 ± 13.3	82.2 ± 8.2
Group ^a					
Consistent (%)	48 (66.7)	37 (77.1)	3 (6.2)	6 (12.5)	2 (4.2)
Inconsistent (%)	24 (33.3)	10 (41.7)	4 (16.7)	7 (29.2)	3 (12.5)

N, numbers of samples; PANSS, Positive and Negative Syndrome Scale.

^aSubjects with medications currently used in “Use as Directed” category were grouped into Consistent group, medications currently used in “Use with caution” or “Use with caution and with frequent blood concentration” categories were grouped into Inconsistent group.

Fisher’s exact test using a two-sided alpha level of 0.05 was performed to examine the relation between the study group and metabolic phenotype of each metabolizing enzyme. None of the three enzymes showed significant correlation to the study group. The test results were $N = 72$, $P = .152$ for CYP1A2, $N = 72$, $P = .44$ for CYP2D6 and $N = 72$, $P = .108$ for CYP3A4.

Target Genotypes

We genotyped the polymorphisms of rs1079597, rs1799978, and rs1799732 on the gene DRD2, rs10042486 on the gene HTR1A, rs1414334 and rs6318 on the gene HTR2C, as well as rs489693 on the gene MC4R.

For the subjects in the “consistent” group, their rs1079597 genotype distribution frequency was 33.3% C/C, 41.7% C/T, and 25% T/T. Their rs1799978 genotype frequency was 4.2% C/C, 33.3% C/T, and 62.5% T/T. Their rs1799732 genotype frequency was 4.2% G/- and 95.8% G/G. Their rs10042486 genotype frequency was 2.1% C/C, 27.1% C/T, and 70.8% T/T. Their rs1414334 genotype frequency was 100% G/G. Their rs6318 genotype frequency was also 100% G/G. Their rs489693 genotype frequency was 29.2% A/C and 70.8% C/C.

For the subjects in the “inconsistent” group, their rs1079597 genotype distribution frequency was 33.3% C/C, 58.3% C/T, and 8.4% T/T. Their rs1799978 genotype frequency was 4.2% C/C, 20.8% C/T, and 75% T/T. Their rs1799732 genotype frequency was 4.2% -/-, 50% G/-, and 45.8% G/G. Their rs10042486 genotype frequency was 8.4% C/C, 45.8% C/T, and 45.8% T/T. Their rs1414334 genotype frequency was 95.8% G/G and 4.2% C/G. Their rs6318 genotype frequency was also 95.8% G/G and 4.2% C/G. Their rs489693 genotype frequency was 4.2% A/A, 20.8% A/C, and 75% C/C. Fisher’s exact test using two-sided alpha level of 0.05 was conducted to examine distribution of genotype according to study groups. Among all 7 SNPs, only rs1799732 on the gene DRD2 was significant, $N = 72$, $P < .001$. The G allele of rs1799732 was more likely to appear in the consistent group (Supplementary Table 3).

Treatment Effectiveness

As indicated in Table 3, the 48 participants in the consistent group ($M = 84.3$, $SD = 12.4$) and 24 participants in the inconsistent group ($M = 81.1$, $SD = 10.5$) demonstrated no

Table 3. Comparison of PANSS Scores at Eight Examining Time Points Between Consistent and Inconsistent Groups

Time Point (Week)	Consistent Group ($N = 48$)		Inconsistent Group ($N = 24$)		<i>t</i>	<i>df</i>	<i>P</i>	Cohen’s <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>				
0	84.3	12.4	81.1	10.5	1.122	53.754	.267 ^a	-0.265
2	81.9	13.0	75.0	11.9	2.178	70.000	.033	-0.544
4	78.3	12.4	72.5	13.1	1.855	70.000	.068	-0.464
8	73.7	11.7	68.0	11.7	1.940	70.000	.056	-0.485
12	69.3	11.3	66.2	9.9	1.123	70.000	.265	-0.281
16	66.2	11.3	67.1	7.7	-0.397	63.539	.693 ^a	0.087
20	59.3	14.4	65.3	8.8	-2.200	67.081	.031 ^a	0.471
24	58.8	15.3	63.8	10.1	-1.654	64.695	.103 ^a	0.361

Note: PANSS, Positive and Negative Syndrome Scale. Baseline was defined as Week 0.

^aF-test is significant ($P < .05$), suggesting a violation of the equal variance assumption. Welch’s two-sample *t*-test was used.

significant difference in the PANSS score ($t[53.754] = 1.122$, $P = .267$) at the baseline level.

Surprisingly, the PANSS scores for the subjects in the “inconsistent” group dropped faster than for those in the “consistent” group (Table 3). At Week 2, the 48 participants in the consistent group ($M = 81.9$, $SD = 13.0$) and 24 participants in the inconsistent group ($M = 75.0$, $SD = 11.9$) had shown a significant difference in PANSS score ($t[70] = 2.178$, $P = .033$). This phenomenon is statistically significant at Week 2 (two weeks after the baseline check), notable but not statistically significant at Week 4 (four weeks after), Week 8 (eight weeks after), and Week 12 (twelve weeks after). The trend starts to reverse after that (see also Supplementary Figure 1).

After Time Point 6 (16 weeks after the baseline level), the PANSS scores for the subjects in the “consistent” group start to get lower than for those in the “inconsistent” group, although it is statistically insignificant at that point. However, the trend becomes more obvious after that. At Time Point 7 (20 weeks after), the consistent group ($M = 59.3$, $SD = 14.4$) and the inconsistent group ($M = 65.3$, $SD = 8.8$) showed a significant difference in the PANSS score ($t[67.081] = -2.200$, $P = .031$). At Time Point 8 (24 weeks after), the consistent group ($M = 58.8$, $SD = 15.3$) and the inconsistent group ($M = 63.8$, $SD = 10.1$) showed a notable but statistically insignificant difference in the PANSS score ($t[64.695] = -1.654$, $P = .103$).

We also examined the PANSS change rate in the two study groups. The results in Table 4 suggest that at Time Point 7, the 48 participants in the consistent group ($M = 55.5$, $SD = 35.0$) had a better PANSS change rate than the 24 participants in the inconsistent group ($M = 34.1$, $SD = 30.0$) ($t[70] = 2.569$, $P = .012$). At Time Point 8, the consistent ($M = 56.1$, $SD = 37.7$) and the inconsistent group ($M = 37.6$, $SD = 33.1$) still demonstrated a significant difference in PANSS change rate ($t[70] = 2.042$, $P = .045$). As expected, participants in the consistent group had

higher PANSS change rate than those in the inconsistent group (see also Supplementary Figure 2).

In Table 5, participants in both consistent and inconsistent groups were categorized into two PANSS drop groups according to a PANSS drop percentage of 25%, 50%, or 75%. Two-sided Fisher’s exact test was performed to examine the association between the study group and the PANSS drop group. Participants in the consistent group were more likely to reach a PANSS drop percentage greater than 50% ($N = 72$, $P = .029$) or 75% ($N = 72$, $P = .025$). This indicated a better response to treatment in the consistent group than in the inconsistent group.

In our algorithmic design, most drugs are put in the “Use with caution” or “Use with caution and with frequent blood concentration monitoring” categories because of their potential adverse reactions or because the patient was either an ultra-rapid or a poor metabolizer for those drugs. Therefore, while it may sound surprising, it is still understandable that antipsychotics in these categories were also effective, since the PANSS score was the only index we considered in this study. However, our results indicate that over the longer term, it is still those who were initially in the “Use as directed” category that show better treatment efficacy. The reasons may lie in the fact that the genetic profiles of those subjects in the “Use as directed” category were matched better with their drug use, or because in actual practice, subjects who were in the “Use with caution” or “Use with caution and with frequent blood concentration monitoring” categories did not actually receive the adequate monitoring that we had recommended.

DISCUSSION

The cytochrome P450 (CYP450) enzyme system is one of the crucial drug metabolic systems in the human body and can oxidize and metabolize exogenous substances including drugs. Various isozymes of CYP450 are involved in the

Table 4. Comparison of PANSS Change Rate (%) Between Consistent and Inconsistent Groups at Each Examining Time Point

Time Point (Week)	Consistent Group (N = 48)		Inconsistent Group (N = 24)		t	df	P	Cohen’s d
	M	SD	M	SD				
2	3.3	30.7	15.5	15.8	-2.237	69.914	.028 ^a	0.458
4	11.7	28.7	22.5	22.2	-1.607	70.000	.113	0.402
8	21.4	25.7	31.9	24.2	-1.664	70.000	.101	0.416
12	33.1	26.0	36.5	20.3	-0.565	70.000	.574	0.141
16	40.1	27.5	30.4	27.2	1.419	70.000	.160	-0.355
20	55.5	35.0	34.1	30.0	2.569	70.000	.012	-0.642
24	56.1	37.7	37.6	33.1	2.042	70.000	.045	-0.511

Note: PANSS, Positive and Negative Syndrome Scale. PANSS change rate was defined as $(\text{PANSS}_{\text{baseline}} - \text{PANSS}_{\text{examining time point}}) / (\text{PANSS}_{\text{baseline}} - 30)$. $\text{PANSS}_{\text{baseline}}$ was defined as Week 0.

^aF-test is significant ($P < .05$), suggesting a violation of the equal variance assumption. Welch’s two-sample *t*-test was used.

Table 5. Analysis of Association Between Groups and PANSS Drop Percentages after 20-week Treatment

PANSS Drop (%)	Group ^a		<i>P</i> ^b
	Consistent	Inconsistent	
≥ 25	34	15	.593
< 25	14	9	
≥ 50	19	3	.029
< 50	29	21	
≥ 75	10	0	.025
< 75	38	24	

Note: PANSS, Positive and Negative Syndrome Scale. PANSS drop percentages was defined as $(\text{PANSS}_{\text{baseline}} - \text{PANSS}_{\text{week 20}}) / (\text{PANSS}_{\text{baseline}} - 30)$.

^aSubjects whose medications currently used in “Use as Directed” category were grouped into Consistent group, medications currently used in “Use with caution” or “Use with caution and with frequent blood concentration” categories were grouped into Inconsistent group.

^bFisher’s exact test was used to obtain *P*-values.

metabolism of psychiatric drugs, mainly including CYP2D6, CYP2C19, CYP2C9, CYP3A4/5 and CYP1A2.²⁴ Among them, CYP2D6 is probably the most important.^{21,25-27} CYP2D6*10 is a high-frequency mutation in the Chinese population that leads to a decrease in enzyme activity, which may increase the blood concentration and peak value of drugs metabolized by CYP2D6 and affect the therapeutic effectiveness and toxic side effects. Copy number variation (CNV) of CYP2D6 is another factor which may greatly change a person’s drug metabolizing ability.²⁸ The polyploidy frequency of the CYP2D6 gene reaches up to 45% in Asians²⁹ and creates a higher occurrence frequency of ultra-rapid metabolizers than in Caucasians (around 7%).²⁸ This is not reflected in our data because the design of our program heavily penalized those ultra-rapid metabolizers, which means they would almost certainly be placed in the “Use with caution” or “Use with caution and with frequent blood concentration monitoring” categories. As a matter of fact, among the 4 SGAs used in the final study, the CYP2D6 genotypes were only considered in the placement of aripiprazole, based on FDA recommendations. The metabolic process of quetiapine is mainly regulated by CYP3A4/5 activity.^{30,31} For clozapine and olanzapine, the gene-drug interaction may exist, even though the reports in current literature regarding this issue are inconclusive²² and no CYP2D6 testing is recommended. CYP1A2 also regulates the metabolism of some antipsychotics including olanzapine.³²⁻³⁵ CYP1A2*1F and CYP1A2*1C are important mutation types in East Asian populations. The CYP1A2*1F mutation will increase the metabolic activity of the CYP1A2 enzyme, while CYP1A2*1C will decrease the metabolic activity of CYP1A2.³⁶ The occurrence frequency of CYP1A2*1F mutation can reach up to 40% or above; therefore, it is not surprising that so many subjects in this study were CYP1A2 ultra-rapid metabolizers.

DRD2 is a dopamine receptor targeted by many antipsychotics.³⁷⁻⁴⁰ The polymorphisms of rs1079597,

rs1799732, and rs1799978 can affect the efficacy of various antipsychotics. MC4R is a melanocyte-stimulating hormone receptor, which plays an important role in controlling weight gain. Weight gain is a common side effect of second-generation antipsychotics, and the single nucleotide polymorphism site rs489693 of MC4R is associated with the weight-gain side effects of multiple antipsychotics.⁴¹⁻⁴³ HTR1A is the serotonin receptor and the target of some antipsychotic drugs such as quetiapine.^{44,45} The genetic polymorphisms on the gene HTR2C may be associated with a patient’s risk for antipsychotic-induced weight gain.⁴⁶ Therefore, the accurate genotyping results for these gene loci will provide an important basis for clinical doctors to prescribe individualized medication.

We noticed, however, that in this practice, most of the subjects who completed the clinical study were treated with clozapine. The association between clozapine therapy and pharmacogenetic testing was less robust than other antipsychotics. Other than the rs489693 site of MC4R, evidence levels supporting most of the other reported genetic polymorphisms were weak, for example, sites on the genes ABCB1.⁴⁷ This is probably one of the reasons why treatment received by both the subject groups, whether consistent or inconsistent with their genetic test reports, was shown to be effective according to the improvement of their PANSS scores.

This clinical study was conducted in Hulunbuir, a prefecture of Inner Mongolia Autonomous Region, China. Ethnic difference was one of the research goals we had in mind when the study was initially designed. However, we ultimately decided to leave out all ethnic minority groups, including Mongol, Manchu, Oroqen, Ewenki, Daur, Hui, and others, because the number of subjects in these groups were not large enough to get statistically meaningful results.

The results obtained in this study demonstrate that genetic testing is useful in guiding the treatment of schizophrenia, although this trial should just be considered a beginning. The number of subjects who finished the entire study is low, and we only used PANSS as the evaluation criterion. As a matter of fact, there are quite a few other indexes, such as RSESE (A Rating Scale for Extrapyrarnidal Side Effects) and UKU Side Effect Rating Scale, that can be used to evaluate the side effects of the prescribed drugs. We may also include pharmacoeconomic measures to indicate the cost saved with guided medication versus unguided medication. In the near future, we plan to carry out a larger-scale, randomized, multi-center, double-blind study to further validate the hypothesis that schizophrenia treatment guided by this program will be more effective than the unguided treatment.

CONCLUSION

Precision medicine is the trend for future medical practice. While there were already quite a few successful reports

about the pharmacogenomic-based genetic test guiding the treatment for psychiatric diseases in North American and European clinical services,¹⁰⁻¹⁸ there were still voices in China arguing against it.⁴⁸ One major practical conclusion we can derive from this study is that treatment for patients whose genetic profiles match their medication tends to show better efficacy in the long term. This is in addition to other benefits which are not reflected in this study, such as lower ADR risks and heightened awareness for blood concentration monitoring. Therefore, genetic testing is highly recommended for those receiving antipsychotic medications for treatment of schizophrenia.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of H2018-051).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.S.; Design - Y.S., X.Z.; Supervision - Y.S., X.Z.; Resource - Y.S., X.Z.; Materials - X.Z., D.Q.; Data Collection and/or Processing - X.G., D.Q.; Analysis and/or Interpretation - X.G., Y.S., C.H., Y.Z.; Literature Search - X.G., Y.S., C.H., Y.Z.; Writing - Y.S., X.G.

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Supplementary Table 1. The included drugs, genes and loci

No.	Drug Name	Gene	Loci
1	Amisulpride	MC4R	rs489693
		DRD2	rs1079597
2	Aripiprazole	CYP2D6	*1, *2A, *2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, CNV
		CYP3A4	*1, *20
		DRD2	rs1799732
		MC4R	rs489693
3	Clozapine	CYP1A2	*1, *1C, *1E, *1F, *1K, *3, *4, *6, *7, *8, *11, *15, and *16
		DRD2	rs1799732
		MC4R	rs489693
		HTR2C	rs1414334
4	Olanzapine	CYP1A2	*1, *1C, *1E, *1F, *1K, *3, *4, *6, *7, *8, *11, *15, and *16
		DRD2	rs1799732
		MC4R	rs489693
		HTR2C	rs1414334
5	Paliperidone	DRD2	rs1799978
		MC4R	rs489693
		HTR2C	rs1414334
6	Quetiapine	CYP3A4	*1, *20
		HTR1A	rs10042486
		MC4R	rs489693
7	Risperidone	CYP2D6	*1, *2A, *2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, CNV
		DRD2	rs1799978
		MC4R	rs489693
		HTR2C	rs1414334
8	Ziprasidone	DRD2	rs1799978
		MC4R	rs489693
		HTR2C	rs1414334
9	Haloperidol	CYP2D6	*1, *2A, *2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, CNV
		CYP3A4	*1, *20
		MC4R	rs489693
10	Perphenazine	CYP2D6	*1, *2A, *2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, CNV
11	Thioridazine	CYP1A2	*1, *1C, *1E, *1F, *1K, *3, *4, *6, *7, *8, *11, *15, and *16
		CYP2D6	*1, *2A, *2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, CNV
12	Zuclopenthixol	CYP2D6	*1, *2A, *2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, CNV
13	Sulpiride	DRD2	rs1799732
		HTR2C	rs6318
14	Loxapine	DRD2	rs1799732
		CYP2D6	*1, *2A, *2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, CNV
15	Chlorpromazine	DRD2	rs1799732
		CYP2D6	*1, *2A, *2, *3, *4, *5, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *36, *41, CNV
		CYP1A2	*1, *1C, *1E, *1F, *1K, *3, *4, *6, *7, *8, *11, *15, and *16
16	Perospirone	CYP3A4	*1, *20

Supplementary Table 2. Distribution of Metabolic Phenotype by Treatment Group

Gene	Metabolic Phenotype	Group		p ^a
		Consistent	Inconsistent	
CYP1A2	UM	18	12	0.152
	EM	30	11	
	IM	0	1	
	PM	0	0	
CYP2D6	UM	0	0	0.44
	EM	30	12	
	IM	17	11	
	PM	1	1	
CYP3A4	UM	0	0	0.108
	EM	48	22	
	IM	0	2	
	PM	0	0	

Note: CYP1A2, cytochrome P450 1A2 gene; CYP2D6, cytochrome P450 2D6 gene; CYP3A4, cytochrome P450 3A4 gene; UM, Ultra-rapid Metabolizer; EM, Extensive Metabolizer; IM, Intermediate Metabolizer; PM, Poor Metabolizer.

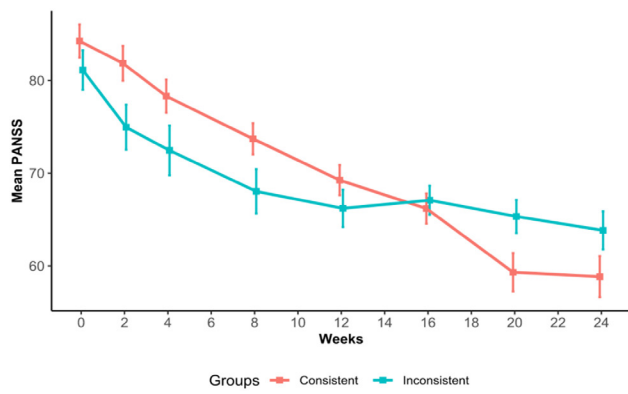
^aP-values were obtained by Fisher's exact test.

Supplementary Table 3. Distribution of Drug Efficacy and Adverse Reaction Related Loci by Treatment Group

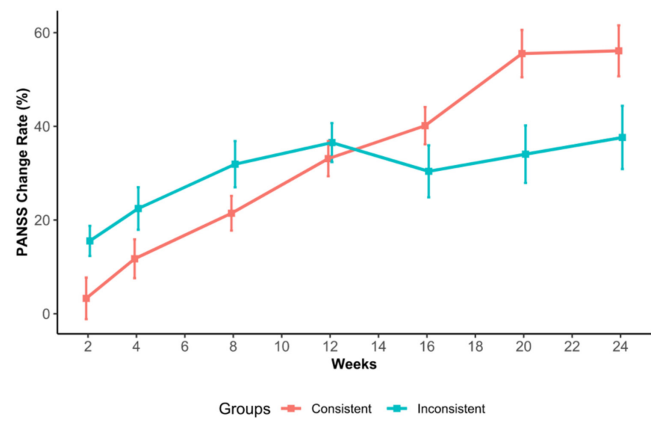
Gene / SNP	Genotype	Group		p ^a
		Consistent	Inconsistent	
DRD2 / rs1079597	C/C	16	8	0.211
	C/T	20	14	
	T/T	12	2	
DRD2 / rs1799978	C/C	2	1	0.61
	C/T	16	5	
	T/T	30	18	
DRD2 / rs1799732	-/-	0	1	<0.001
	G/-	2	12	
	G/G	46	11	
HTR1A / rs10042486	C/C	1	2	0.073
	C/T	13	11	
	T/T	34	11	
HTR2C / rs1414334	C/C	0	0	0.333
	C/G	0	1	
	G/G	48	23	
HTR2C / rs6318	C/C	0	0	0.333
	C/G	0	1	
	G/G	48	23	
MC4R / rs489693	A/A	0	1	0.365
	A/C	14	5	
	C/C	34	18	

Note: DRD2, dopamine 2 receptor gene; HTR1A, 5-Hydroxytryptamine Receptor 1A gene; HTR2C, 5-Hydroxytryptamine Receptor 2C gene; MC4R, melanocortin4 receptor gene. SNP, single nucleotide polymorphism site.

^aP-values were obtained by Fisher's exact test.



Supplementary Figure 1. PANSS scores at each time points for the two groups. Points represent mean of PANSS scores of each group at each time point. Bars represent SEM. NSS: Positive and Negative Syndrome Scale. 0 week was defined as baseline.



Supplementary Figure 2. PANSS change rate at each time points for the two groups. Points represent mean of PANSS change rate of each group at each time point. Bars represent SEM. PANSS change rate was defined as $(PANSS_{baseline} - PANSS_{examining\ time\ point}) / (PANSS_{baseline} - 30)$. $PANSS_{baseline}$ was defined as 0 week.