PATHWAY GENOMICS®

Mental Health DNA Insight®

WHITE PAPER

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Pathway Genomics' Mental Health DNA Insight® test is aimed to help psychiatrists, neurologists, and other physicians in identifying optimal psychotropic medications for their patients by incorporating genetic information into their clinical decision making.

Introduction

Pharmaceutical innovation during the past several decades has empowered psychiatrists and other clinicians with a large inventory of medications for treating depression, bipolar disorder, schizophrenia and other mental health conditions. However, response to these medications is known to have remarkable interindividual variation, even when the same drug is used at the same dose[1]. Clinical benefits of these drugs may be compromised by severe adverse reactions, which contribute significantly to poor patient compliance and high rates of discontinuation[2].

Psychiatrists are tasked with identifying a treatment plan for each patient that is both well-tolerated and effective. While clinical experience plays an indispensable role in choosing psychotropic drugs, treatment optimization remains largely a trial-and-error process[3]. Patients often are prescribed multiple drugs until a suitable one is found. This progression through many drugs can be an especially time consuming process because response to some psychotropic medications, such as SSRIs, cannot be ascertained until 2-4 weeks after the initiation of treatment. Not only is this process expensive, but it also delays the delivery of treatment benefits, and increases the risk of adverse effects and the rate of patient drop-out.

Genetic factors play an important role in how an individual responds to various drugs[4-8]. As indicated in Figure 1, the plasma levels of a drug are directly associated with the activity of the enzymes that metabolize the medication. With personalized pharmacogenetic results provided by the Mental Health DNA Insight® test, a physician may expedite the process of finding a safe and effective medication. This test may also identify drugs that better meet the patient's needs but have been overlooked or are not on the physician's typical formulary. In addition, personalized drug dosing using an understanding of the individual's genetics make up helps achieve the optimal clinical effect of the medication. For example, Figure 2 depicts dosing regimens for the antidepressant nortriptyline based on patients' CYP2D6 activity (stratified as Poor Metabolizers, Intermediate Metabolizers, Extensive Metabolizers and Ultrarapid Metabolizers) compared to the typically prescribed regimen based only on population-wide recommendations. While this test can assist in the prioritization of drugs for a new patient, it can also provide insights into treatment-resistant cases in which patients are found to be non-responsive to multiple drugs.

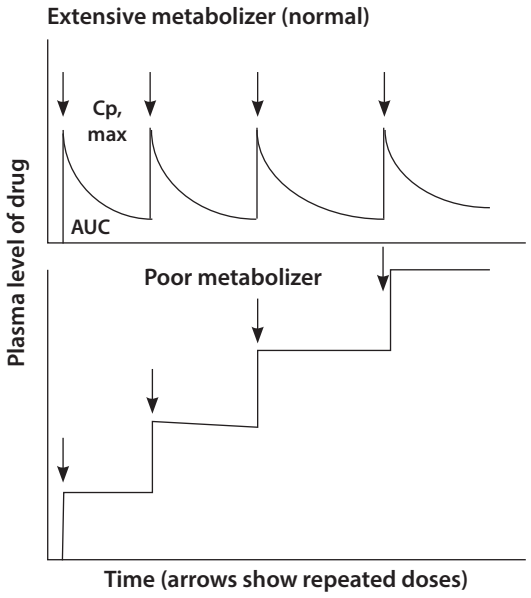

Figure 1: Variation in CYP activities has an impact on drug pharmacokinetics (Guengerich, 2006[9]).

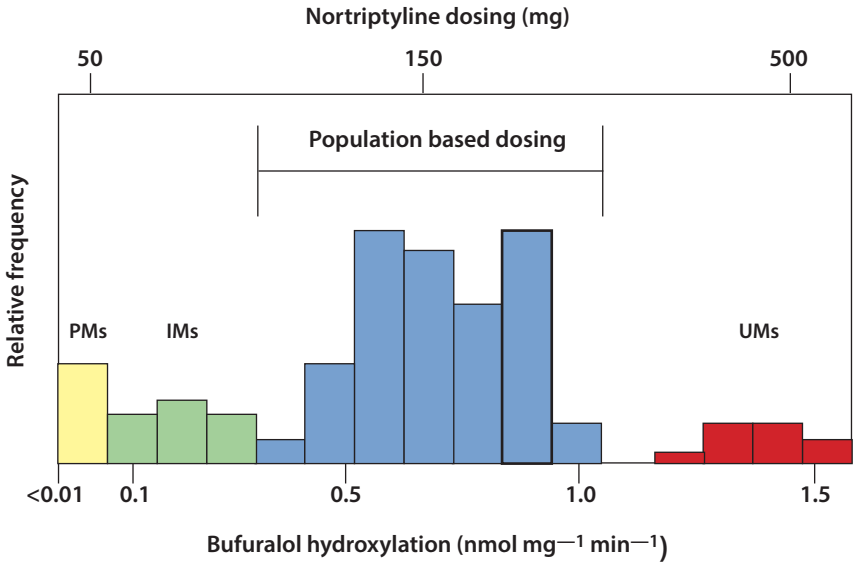

Figure 2: Variation in CYP2D6 activity (analyzed by hydroxylation of bufuralol) and corresponding nortriptyline dosing in the Caucasian population (Ingelman-Sundberg, 2004[10]). PMs – Poor Metabolizers, IMs – Intermediate Metabolizers, and UMs – Ultrarapid Metabolizers.

Clinical Validity of Pharmacogenomic Testing

Recent technological breakthroughs provide support for the clinical validity of genomic testing in predicting drug efficacy and side effects. Scientific staff (Ph.D. and M.D. level) at Pathway Genomics® routinely review published clinical studies and case reports to keep our products updated. The most current information allows us to determine whether genetic variations are associated with pharmacokinetic (PK) or pharmacodynamics (PD) responses to mental health medications. Analysis of over 300 up-to-date publications reveals statistically significant associations of genetic variations in the CYP2C19, CYP2D6, CYP2C9, CYP1A2, CYP2B6, CYP3A4, CYP3A5, UGT1A4, SLC6A4, HTR2A, HTR2C, HLA-A, HLA-B, and POLG genes with PK and/or PD responses to more than 50 widely prescribed psychiatric medications. An updated technical bulletin containing a comprehensive reference list of original studies is available upon request.

These PK and/or PD outcomes provide physicians a powerful tool to assess individual differences in drug efficacy and likelihood of side effects. For example, CYP2C19 and CYP2D6 genotypes show a great correlation with PK profiles, leading to variations in drug blood levels and efficacy; while SLC6A4 and HTR2C genotypes correlate with PD profiles, affecting therapeutic benefits and risk of adverse reactions.

In summary, numerous lines of clinical evidence strongly support the validity of pharmacogenomics testing to assist healthcare providers in predicting the metabolism, safety, and efficacy of medications commonly used for the treatment of depression, bipolar disorder, schizophrenia and other mental health conditions.

FDA and Pharmacogenomics

The clinical value of pharmacogenomic information is increasingly being recognized by regulatory agencies such as the FDA and EMA. The FDA requires pharmacogenomic information on the label of over 150 drugs including many drugs used in the management of mental health. A partial list includes widely prescribed medications such as Celexa® (citalopram), Abilify® (aripiprazole), Paxil® (paroxetine), Effexor® (venlafaxine), and Tegretol® (carbamazepine). A complete list of drugs currently required to provide pharmacogenomic information on the medication label or insert can be found at http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ Pharmacogenetics/ucm083378.htm.

The Assay Panel

The assay panel of Mental Health DNA Insight® was developed based on a comprehensive and in-depth review of current medical literature. This test reflects the most up-to-date understanding of genetic influences in the metabolism, adverse reactions, and therapeutic effects of psychiatric medications. For CYP2D6 and CYP2C19, two essential genes in the metabolism of many psychotropic medications, we test for alleles that have a combined frequency of over 95% and 99%, respectively, in major ethnic groups.

Mental Health DNA Insight® Assay Panel

Gene	Function	Variants tested	Clinical relevance
CYP2D6	An enzyme involved in drug metabolism	*1, *1xN, *2, *2xN, *3, *4, *4xN, *5, *6, *6xN, *7, *8, *9, *10, *10xN, *11, *12, *14A, *15, *17, *17xN, *29, *35, *36, *36-*10, *36xN, *41, *41xN	CYP2D6 enzyme activity can be predicted based on genetic variation in the CYP2D6 gene. Activity of the enzyme plays an important role in metabolizing many antidepressants and antipsychotics currently in use, resulting in variations in their therapeutic and adverse effects. An individual can be classified as a poor metabolizer, an intermediate metabolizer, an extensive metabolizer or an ultrarapid metabolizer according to his/her CYP2D6 activity.
CYP2C19	An enzyme involved in drug metabolism	*1, *2, *3, *4, *5, *6, *7, *8, *17	CYP2C19 enzyme activity, which can be predicted by genetic tests, has primary influence in the metabolism of some antidepressants, leading to variations in drug blood levels, efficacy and adverse response. An individual can be classified as a poor metabolizer, an intermediate metabolizer, an extensive metabolizer or an ultrarapid metabolizer according to his/her CYP2C19 activity.
CYP2C9	An enzyme involved in drug metabolism	*1, *2, *3, *6	CYP2C9 enzyme activity can be predicted based on genetic variation in the CYP2C9 gene. Activity of the enzyme plays an important role in metabolizing some mood stabilizers and anticonvulsants such as phenytoin, resulting in variations in their therapeutic and adverse effects. An individual can be classified as a poor metabolizer, an intermediate metabolizer or an extensive metabolizer according to his/her CYP2C9 activity.
CYP1A2	An enzyme involved in drug metabolism	*1F	CYP1A2 is a major enzyme in the metabolism of olanzapine and clozapine. Genetic variation in CYP1A2 influences plasma concentrations of these medications.
CYP2B6	An enzyme involved in drug metabolism	*1, *2, *4, *5, *6, *9, *18	CYP2B6 enzyme activity can be predicted based on genetic variation in the CYP2B6 gene. Activity of the enzyme plays an important role in metabolizing antidepressants such as bupropion, resulting in variations in plasma concentrations of a major bupropion metabolite. An individual can be classified as a poor metabolizer, an intermediate metabolizer or an extensive metabolizer according to his/her CYP2B6 activity.

CYP3A4	An enzyme involved in drug metabolism	*1, *4, *5, *6, *20, *22, *26	Genetic variations in the CYP3A4 gene may affect the CYP3A4 enzymatic activity, which plays an important role in metabolizing some antidepressants.
CYP3A5	An enzyme involved in drug metabolism	*3	CYP3A5 enzyme expression can be predicted based on genetic variation in the CYP3A5 gene. Expression of the enzyme plays an important role in metabolizing alprazolam. The CYP3A5*3 genotype affected the disposition of alprazolam and thus influenced the plasma levels and oral clearance of alprazolam.
UGT1A4	An enzyme involved in drug metabolism	rs2011425 (L48V)	The rs2011425 polymorphism in the UGT1A4 gene alters the activity of the encoded enzyme, which mediates the metabolism of a number of psychotropic medications.
SLC6A4 (SERT)	Serotonin transporter; a target of antidepressants	5-HTTLPR, rs25531	Polymorphisms in the promoter region of the SLC6A4 gene have been shown to affect therapeutic benefits and risk of adverse reactions in patients treated with some antidepressants.
HTR2A (5-HT2A)	A receptor for serotonin	rs7997012, rs6311 (-1438G>A)	Genetic variants in HTR2A are associated with citalopram response and risk of adverse effects to fluvoxamine and paroxetine.
HTR2C (5-HT2C)	A receptor for serotonin	rs3813929, rs1414334	The rs3813929 and rs1414334 polymorphisms in the promoter of the HTR2C gene significantly influence weight gain associated with the use of atypical antipsychotics.
HLA-B	Part of the human leukocyte antigen (HLA) complex involved in immunity	Proxy SNPs of HLA-B*1502 allele (rs3909184 and rs2844682	The HLA-B*1502 variant is associated with phenytoin hypersensitivity leading to an increased risk of developing serious skin reactions. Patients may also be advised to avoid related mood stabilizers and anticonvulsants such as carbamazepine, lamotrigine and oxcarbazepine. This genetic association is most applicable to patients of Han Chinese descent.
HLA-A	Part of the human leukocyte antigen (HLA) complex involved in immunity	A proxy SNP of HLA-A*3101 allele (rs1061235)	The HLA-A*3101 gene variant is associated with carbamazepine hypersensitivity leading to an increased risk of developing serious skin reactions.
POLG	A protein essential for mitochondrial DNA replication	rs113994097, rs113994095, rs113994098	Genetic variants in POLG gene are associated with valproic acid and divalproex-induced acute liver failure and resultant death.

Possible Outcomes

Pathway Genomics' Mental Health DNA Insight® test provides personalized pharmacogenetic information and displays patient's results in a color-coded chart based on the individual's genotypes and recommendation categories. The four recommendation categories are listed below:

- → **Preferential Use:** The drug is likely to have better-than-average therapeutic benefits and/or lower-than-average adverse effect risk when used in the tested patient
- → **Use as Directed:** The drug is likely to have typical therapeutic and adverse effects when used in the tested patient.
- → **May Have Significant Limitations:** The drug is likely to have lower-than-average therapeutic benefits and/or higher-than-average adverse effect risk when used in the tested patient.
- → **May Cause Serious Adverse Events:** The drug is likely to induce severe adverse reactions when used in the tested patient. Close monitoring or alternative medications are strongly recommended.

Psychiatric Medications Covered

Antidepressants	Antipsychotics	Mood stabilizers
amitriptyline	aripiprazole	carbamazepine
bupropion	asenapine	divalproex
buspirone	clozapine	lamotrigine
citalopram	haloperidol	oxcarbazepine
clomipramine	iloperidone	phenytoin
desipramine	lurasidone	valproic acid
doxepin	olanzapine	
duloxetine	paliperidone	**Benzodiazepines**
escitalopram	perphenazine	alprazolam
fluoxetine	pimozide	clobazam
fluvoxamine	quetiapine	diazepam
imipramine	risperidone	
levomilnacipran	thioridazine	**Other neurological medications**
mirtazapine	ziprasidone	dextromethorphan and quinidine
nefazodone	zuclopenthixol	galantamine
nortriptyline		modafinil
paroxetine		tetrabenazine
protriptyline		
sertraline		**NE reuptake inhibitor (ADHD medication)**
trazodone		
trimipramine		atomoxetine
venlafaxine		
vilazodone		
vortioxetine		

Summary

Mental Health DNA Insight® offers a package of genetic tests and a clear, interpretive report, aiming to contribute to the development of personalized psychiatric treatment. Our goals are:

→ Expedite treatment optimization

→ Improve patient compliance by reducing adverse effects and increasing therapeutic benefits

→ Reduce the risk of adverse events, lack of treatment response and inpatient care

References Cited

1. Kirchheiner, J., A. Seeringer, and R. Viviani, *Pharmacogenetics in psychiatry--a useful clinical tool or wishful thinking for the future?* Curr Pharm Des, 2010. **16**(2): p. 136-44.
2. Malhotra, A.K., J.P. Zhang, and T. Lencz, *Pharmacogenetics in psychiatry: translating research into clinical practice.* Mol Psychiatry, 2012. **17**(8): p. 760-9.
3. Petersen, T., et al., *A survey of prescribing practices in the treatment of depression.* Prog Neuropsychopharmacol Biol Psychiatry, 2002. **26**(1): p. 177-87.
4. Narasimhan, S. and F.W. Lohoff, *Pharmacogenetics of antidepressant drugs: current clinical practice and future directions.* Pharmacogenomics, 2012. **13**(4): p. 441-64.
5. Leckband, S.G., et al., *Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing.* Clin Pharmacol Ther, 2013. **94**(3): p. 324-8.
6. Hicks, J.K., et al., *Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants.* Clin Pharmacol Ther, 2013. **93**(5): p. 402-8.
7. Kirchheiner, J., et al., *CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages.* Acta Psychiatr Scand, 2001. **104**(3): p. 173-92.
8. Zhang, J.P. and A.K. Malhotra, *Pharmacogenetics and antipsychotics: therapeutic efficacy and side effects prediction.* Expert Opin Drug Metab Toxicol, 2011. **7**(1): p. 9-37.
9. Guengerich, F.P., *Cytochrome P450s and other enzymes in drug metabolism and toxicity.* AAPS J, 2006. **8**(1): p. E101-11.
10. Ingelman-Sundberg, M., *Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future.* Trends Pharmacol Sci, 2004. **25**(4): p. 193-200.

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