GeneSight® Psychotropic and GeneSight® MTHFR Case Study

Being confident about treatment: 43 year old man with depression and anxiety

Background

Behavioral health drug selection and dosing is a trial and error process that often leads to delayed response time, frustration and increased medical costs. There is a high degree of variability in response to behavioral health medications, some of which is due to individual genetics. Assurex Health utilizes its GeneSight® proprietary CPGx® combinatorial pharmacogenomics technology to understand how unique inherited traits might influence a patient's response to medication. GeneSight Psychotropic is a pharmacogenomic test developed to help clinicians select medications commonly prescribed to treat behavioral health conditions. There have been multiple studies published in peer reviewed journals addressing the clinical utility of GeneSight Psychotropic.[1-4]

Patient

- Patient is a 43 year old male with major depressive disorder, panic disorder, agoraphobia, generalized anxiety disorder and cluster B traits.
- Target symptoms include: irritability, anxiety, obsessive concern about bed bug contamination, and depressed mood; initial PHQ-9 was 25.
- Past medical history: No chronic illness.
- Social history: No use of drugs, alcohol, or tobacco.
- Psychiatric medication history: Patient has been on sertraline (Zoloft®), citalopram (Celexa®), escitalopram (Lexapro®), bupropion (Wellbutrin®), venlafaxine (Effexor®), and duloxetine (Cymbalta®). He possibly had hives on the bupropion. He reports that other medications have not been effective.
- Medications at the time of GeneSight testing: None.
- **The physician ordered GeneSight as a way to utilize the pharmacogenomic information to help streamline the medication regimen and support the "next steps" in treatment.**

GeneSight Psychotropic Results

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
amitriptyline (Elavil®)	citalopram (Celexa®) [1,4]	duloxetine (Cymbalta®) [2,7]
bupropion (Wellbutrin®)	escitalopram (Lexapro®) [1,4]	fluvoxamine (Luvox®) [2,7]
clomipramine (Anafranil®)	sertraline (Zoloft®) [4]	mirtazapine (Remeron®) [2,7]
desipramine (Norpramin®)		paroxetine (Paxil®) [4,6]
desvenlafaxine (Pristiq®)		
doxepin (Sinequan®)		
fluoxetine (Prozac®)		
imipramine (Tofranil®)		
levomilnacipran (Fetzima®)		
nortriptyline (Pamelor®)		
selegiline (Emsam®)		
trazodone (Desyrel®)		
venlafaxine (Effexor®)		
vilazodone (Viibryd®)		
vortioxetine (Brintellix®)		

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
aripiprazole (Abilify®)	chlorpromazine (Thorazine®) [2,7]	olanzapine (Zyprexa®) [2,7]
asenapine (Saphris®)	clozapine (Clozaril®) [2,7]	thiothixene (Navane®) [2,7]
fluphenazine (Prolixin®)	haloperidol (Haldol®) [2,7]	
iloperidone (Fanapt®)	thioridazine (Mellaril®) [2,7]	
lurasidone (Latuda®)		
paliperidone (Invega®)		
perphenazine (Trilafon®)		
quetiapine (Seroquel®)		
risperidone (Risperdal®)		
ziprasidone (Geodon®)		

[1]: Serum level may be too high, lower doses may be required.
[2]: Serum level may be too low, higher doses may be required.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[6]: Use of this drug may increase risk of side effects.
[7]: Serum level may be too low in smokers.

All psychotropic medications require clinical monitoring.
Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed.

GeneSight MTHFR Results

NORMAL FOLIC ACID CONVERSION	REDUCED FOLIC ACID CONVERSION	SIGNIFICANTLY REDUCED FOLIC ACID CONVERSION
		✓

Note: Serum levels of folate may be too low. Folate supplementation or higher daily intake of folic acid may be required.

Patient Genotype and Phenotype

MTHFR	Reduced Activity	T/T
This individual is homozygous for the T allele of the C677T polymorphism in the MTHFR gene. This genotype is associated with significantly reduced folic acid metabolism, significantly decreased serum folate levels, and significantly increased homocysteine levels.		

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GeneSight Psychotropic Results (continued)

The patient's genetic results for each of the genes were identified as:

CYP2D6	Extensive Metabolizer	*1/*1
CYP2C19	Intermediate Metabolizer	*1/*2
CYP2C9	Extensive Metabolizer	*1/*1
CYP3A4	Extensive Metabolizer	*1/*1
CYP2B6	Extensive Metabolizer	*1/*1
CYP1A2	Ultrarapid Metabolizer	-163 C>A - A/A, 5347C>T - T/T
SLC6A4	Intermediate Response	L/S
HTR2A	Reduced Activity	G/G
MTHFR	Reduced Activity	T/T

Pharmacogenomic Insight

The methylenetetrahydrofolate reductase (MTHFR) enzyme converts synthetic folic acid and dietary folate into its active form, L-methylfolate, which plays a critical role in neurotransmitter synthesis.[5] Some individuals carry a mutation at the C677T SNP of the MTHFR gene, which results in 35% reduction in activity for heterozygotes (C/T) and a 70% reduction in activity for homozygotes (T/T).[6] Individuals who carry this mutation will have a reduced capacity to create L-methylfolate. There are a variety of ways that clinicians use this information. One option is to increase folic acid supplementation, which compensates for the reduced MTHFR enzyme activity leading to increased folate levels. Another option for patients with reduced MTHFR activity is to directly supplement with oral L-methylfolate. Given the (T/T) genotype in this patient, the physician recommended L-methylfolate for the patient. By bypassing the conversion step mediated by MTHFR, supplementation with L-methylfolate could improve serum and CNS folate levels in individuals with reduced MTHFR activity. The supplementation of L-methylfolate may help increase the production of certain neurotransmitters which is theorized to help improve depression.

Pharmacogenomic-Informed Decision Making

- Four of the six previous antidepressant trials were in the yellow and red advisory category.
- Additionally, the patient was noted to be homozygous for the T allele of the C677T polymorphism in the MTHFR gene—suggesting "reduced activity" for folic acid conversion to the active form (L-methylfolate).
- The healthcare provider elected to start fluoxetine (Prozac®), which is in the use as directed category, in combination with L-methylfolate to target this patient's symptoms.

MEDICATIONS AT TESTING	CHANGE IN MEDICATIONS
None	Started fluoxetine
	Started L-methylfolate

Conclusions

The patient's depression improved. His PHQ-9 went from 25 at time of evaluation to seven about six weeks after starting fluoxetine (and about three weeks after starting L-methylfolate). The physician commented, "I think that the Genesight guided therapy options gave him more confidence in the antidepressant. Also, the information regarding MTHFR status was very valuable. The depression symptoms did markedly improve after starting the L-methylfolate."

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