Does Pharmacogenetic Testing In Psychiatric Populations Influence Clinician Treatment Selection and Confidence?

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Presented at: The International Society for CNS Clinical Trials and Methodology (ISCTM) October 3, 2011

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Background

Response to psychotropic therapy is highly variable and an estimated 30%-50% of treated patients show inadequate response\[1\]. Genetic variations lead to alterations in protein expression that can contribute to disease etiology and treatment variability\[1\].

Pharmacogenetics is the study of the relationship between single nucleotide polymorphisms (SNPs) and drug response\[2\]. Subtle molecular variations resulting from SNPs may lead to changes in CNS signal transduction and treatment variability\[2\].

Genetic tests available for psychiatric disorders are largely limited to pharmacokinetic genes, those related to the metabolism of medications. A noticeable void exists for pharmacogenetic tests which analyze pharmacodynamic genes, those related to interactions of the drug with the body. The extent to which testing for such variations in clinical contexts may influence clinical practice and treatment outcomes has not been established.
Study Objectives

This study aims to demonstrate the distribution of psychiatric disorders among patients selected by their providers to receive pharmacogenetic testing and to examine effects of availability of genetic results on clinician treatment decisions.

Funding

All funding provided by Genomind, LLC.

Acknowledgements

The authors wish to acknowledge Custom Data Shop, LLC for their data preparation and analysis.

Disclosure

One or more authors report potential conflicts which are described in the program: Bryce Kasuba and Rachel Dicker are employed by Genomind, Jay Lombard is an employee of and has equity interests in Genomind, and Roy Perlis serves on the Scientific Advisory Board for Genomind.
Methods

Design: Retrospective, cross-sectional analysis of clinician surveys
Inclusion: Clinician members of the Neuroscience Education Institute (NEI)
  Prescriptive Authority
  Completion of Clinical Decision Survey (CDS) for each patient tested
Exclusion: None
Recruitment: Email invitation to all NEI members
Implementation: Each clinician was supplied with two genetic tests. Patient selection was made at the discretion of the clinician
Sample Collection and Analysis: Simple, non-invasive saliva collection method in clinician's office; samples sent by clinician to a CLIA-certified lab for analysis
Genetic Results Report: (See next page for sample report)
  • DE-IDENTIFIED analytic results report provided to clinicians
  • Psychopharmacology experts available to assist with interpretation
  • Decisions concerning appropriate treatment regimen for patients were solely the responsibility of the clinicians
Data Collection: Clinicians were asked to complete a Clinical Decision Survey (CDS), and follow-up by mail/phone was conducted to reinforce CDS completion

Analysis

CDS responses were analyzed using SAS/STAT software, version 9.2 of the SAS™ system for Windows
**Sample Report**

### Summary of Results

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Gene</th>
<th>Result</th>
<th>Interpretive Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>Serotonin Transporter SLCA4</td>
<td>S/S</td>
<td>Compared to the LA/LA genotype, individuals with the S/S, S/LG, and LG/LG genotypes have decreased serotonin transporter expression, may be less likely to respond to SSRI-based therapy, and may be more likely to experience adverse effects from SSRIs. In individuals with unsatisfactory response to SSRI therapy and who possess the S/S, S/LG, or LG/LG genotypes, treatment with an alternative antidepressant mechanism may be considered. Greater caution is recommended when initiating or discontinuing SSRIs in individuals with the Short (S) or Long (L) alleles. Clinical correlation is suggested.</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Calcium Channel CACNA1C</td>
<td>G/A</td>
<td>Presence of the A allele (G/A or A/A genotypes) has been associated with elevated rates of mood disorder recurrence. This CACNA1C variant has been linked to bipolar disease, treatment-resistant depression and some psychotic states. Higher treatment vigilance may be required in these patients.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Dopamine D2 Receptor DRD2</td>
<td>Ins/Ins</td>
<td>The Ins/Ins genotype has been associated with better antipsychotic drug response compared to Del allele carriers (Ins/Del or Del/Del genotypes).</td>
</tr>
<tr>
<td></td>
<td>Catechol-O-Methyltransferase COMT</td>
<td>Val/Val</td>
<td>The COMT Val allele is a high activity allele. The Val/Val genotype has been associated with decreased presynaptic dopamine. This effect may lead to reduced executive brain function, including cognitive and working memory deficits.</td>
</tr>
<tr>
<td>Methylation</td>
<td>Methylenetetrahydrofolate Reductase MTHFR</td>
<td>C/T</td>
<td>MTHFR is required to convert folic acid to methylfolate. Presence of the 677 T allele (C/T or T/T) is associated with decreased MTHFR activity and may lead to increased homocysteine and decreased methylation capacity.</td>
</tr>
<tr>
<td>Metabolism</td>
<td>MTHFR - COMT methylation interaction</td>
<td>Low methylation</td>
<td>Methylation pathways regulate the metabolism of neurotransmitters, particularly dopamine. In low methylation states, such as that caused by the MTHFR 677 T allele, dopamine is degraded at a higher rate. This effect may be exacerbated in patients who carry both the MTHFR 677 T allele and the high activity COMT 158 Val/Val genotype.</td>
</tr>
<tr>
<td></td>
<td>Cytochrome P450 2D6 CYP2D6</td>
<td>UM or EM</td>
<td>This patient’s genotype is consistent with one of two possible phenotypes (please see page 6): Extensive metabolizers (EMs) represent the norm of metabolic capacity. In general, EMs can be prescribed medications that are metabolized by CYP2D6 following standard dosing practices. Ultra-rapid metabolizers (UMs) exhibit higher than average rates of metabolism. Faster rates of drug metabolism may be associated with side effects or lack of response. UMs are at increased risk of therapeutic failure due to increased drug elimination and may require an increased dosage of medications that are inactivated by CYP2D6. UMs may also be at increased risk of drug-induced side effects due to increased exposure to active drug metabolites, in which case they may require lower than average doses.</td>
</tr>
<tr>
<td></td>
<td>Cytochrome P450 2C19 CYP2C19</td>
<td>UM</td>
<td>Ultra-rapid metabolizers (UMs) exhibit higher than average rates of metabolism. Faster rates of drug metabolism may be associated with side effects or lack of response. UMs are at increased risk of therapeutic failure due to increased drug elimination and may require an increased dosage of medications that are inactivated by CYP2C19. UMs may also be at increased risk of drug-induced side effects due to increased exposure to active drug metabolites, in which case they may require lower than average doses.</td>
</tr>
</tbody>
</table>
Results

- 175 clinicians chose to participate
- Genetic testing was performed for 296 patients
- 69 clinicians returned CDSs related to 105 distinct patients

As a result of the assay report, I have elected to: (n=105)

- Add a second medication
- Change to a different medicine in a different class
- Change the starting dose, or the titration schedule, but keep the same medicine
- Change to a different medicine in the same class
- Make no change
Among clinicians who indicated they did not make a change in medication after receiving the assay report...

Number of clinicians who reported an influence on confidence in treatment decisions (n = 34)
Results (Continued)

Among clinicians who indicated they did not make a change in medication after receiving the assay report...

Number of clinicians who reported an influence on treatment (n = 34)
Results (Continued)

Among all clinicians who provided CDS responses...

Did the assay report influence your confidence in treatment decisions?

(n=105)
Among all clinicians who provided CDS responses...
Results (Continued)

Number of Previous Adequate Treatment Trials (n=102)
Results (Continued)

Last Month-Long Period of Euthymic Mood (n=102)

- 1 month ago: 21%
- 6 months ago: 15%
- 1 year ago: 14%
- 2-4 years ago: 17%
- More than 4 years ago: 13%
- Never: 20%
Conclusions

In patients chosen by their clinicians for genetic testing, 39% were reported as having had four or more previous adequate treatment trials.

76% of clinicians reported that having the genetic assay results influenced their treatment and 87% reported that having the results influenced their confidence in treatment decisions.

Further prospective research is needed to demonstrate utility of this genetic assay as it relates to specific treatment guidance.

References
