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# Memorandum

**To:** PerformCare Provider Network

**From:** Scott Daubert PhD, VP Operations

**Date:** August 1, 2015

**Subject:** PC-17 Pharmacogenomics tests for psychiatric medications

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## Claims Payment and Clinical Policy Clarification

### *Question/Issue:*

The HealthChoices behavioral health program includes coverage for medically necessary mental health, substance abuse and behavioral services. This includes laboratory and diagnostic studies and procedures for the purpose of determining response to behavioral health medication and/or treatment ordered by Behavioral Health Service Providers acting within the scope of their license. Recent questions have been received concerning whether pharmacogenomics tests for psychiatric medications are included.

### *Glossary:*

**Pharmacogenomics—** The study of how an individual's genetic makeup, or genotype, affects the body's response to drugs. Pharmacogenomics as a science examines associations among variations in genes with individual responses to a drug or medication. In application, pharmacogenomic results (i.e., information on the patient's genetic variations) can contribute to predicting a patient's response to a given drug: good, bad or none at all. (CMS definition NCD 90.1)

### *PerformCare Answer/Response:*

PerformCare considers the use of pharmacogenomics tests for psychiatric medications to be investigational and, therefore, not medically necessary, including but not limited to the use of GeneSightRx or PHARMAchip assay genotyping of CYP1A2, CYP2C9, CYP2C19, CYP2D6, HTR2A, and SCL6A4 to help guide administration of antidepressants and antipsychotics or SureGene (STA2R) for antipsychotic drug response.

### *Source Documentation / References:*

**Background**

For decades, clinicians have recognized that patients may respond differently to the same dose of a given pharmaceutical agent. Drugs are approved by the Food and Drug Administration (FDA) for sale based upon the general health improvement across a population and consider individual variations only if a subpopulation experiences significant adverse effects. As more of the human genetic makeup is understood, the goal of "personalized medicine" comes closer to realization. Currently there are a limited number of genomic tests that can impact the physician selection of therapies and significantly impact the patient outcome. Gervasini et al. noted that "despite significant progress in pharmacogenetic research, only a few drugs such as cetuximab, dasatinib, maraviroc, and trastuzumab, require a pharmacogenetic test before being prescribed."

In mental health, there has been the recognition of patterns of behavioral expression, suggesting an inherited predisposition. More exciting has been the hope that genomics can lead to improved selection of pharmacotherapy. Currently physician selection of anti-depressants or anti-psychotic medications has been based upon physician experience with that drug and not on knowledge of patient-specific medication impact.

Several commercially available genomic tests are currently on the market, with more to come. The intentions of these tests are to enhance positive predictors of medication-specific responders. By using genomic information, the hope is that targeted therapy will replace the current "trial-and-error" approach to medication selection. Studies sponsored by the genomic test manufacturers have reported inferred success in targeted therapies. However, un-sponsored researchers, after reviewing the data, have not found sufficient evidence to support the claims that genomic testing results in improved clinical outcomes in the treatment of psychiatric conditions.

**Methods**

**Searches (Apr. 2015):**
PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality's National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

Searches were conducted using the term "pharmacogenomic drugs."

Included were:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings:**
While there have been a number of studies reviewing the statistical association of response to medication in people with varying behavioral health disorders, there are no definitive, validated studies showing that use of pharmacogenomic studies can lead to improved outcomes. In a population there is a greater association of response to specific drug classes (e.g., SSRIs) for the subpopulation with specific behavioral health diagnoses. A number of studies in the published literature are funded by the companies developing these testing tools and/or have principal investigators who are on the boards or are employees of these genetic testing companies. Meta-analyses and multi-centered trials have not demonstrated clear outcome improvements with decisions based upon data from pharmacogenomics test data.

**Summary of clinical evidence:**

| Citation | Content, Methods, Recommendations |
|---|---|
| Niitsu (2013) | **Key Points:**<br>• Meta-analysis from three major reviews.<br>• The findings suggested the BDNF Val66Met as the best single candidate involved in antidepressant response, with a selective effect on SSRI treatment.<br>• Overall results supported no major effect of any single gene variant on AD efficacy. |
| GENDEP (2013) | **Key Points:**<br>• A meta-analysis was performed on data from three genome-wide pharmacogenetic studies (the Genome-Based Therapeutic Drugs for Depression [GENDEP] project, the Munich Antidepressant Response Signature [MARS] project, and the Sequenced Treatment Alternatives to Relieve Depression [STAR*D] study, which included 2,256 individuals of Northern European descent with major depressive disorder.<br>• There were no reliable predictors of antidepressant treatment outcome, although they did identify modest, direct evidence that common genetic variation contributes to individual differences in antidepressant response.<br>. |

**References**

**Professional society guidelines/other:**

American College of Medical Geneticists: ACMG Issues DTC Genetic-Testing Guidelines; http://www.ashg.org/pdf/newsclip/Pharmacogenomics%20Reporter%20-%205.7.08.PDF. Accessed April 8, 2015.

**Peer-reviewed references:**

Ferentinos P, Rivera M, Ising M, et al. Investigating the genetic variation underlying episodicity in major depressive disorder: suggestive evidence for a bipolar contribution. *J Affect Disorders*.2014 Feb;155:81 – 9.

Gardner KR, Brennan FX, Scott R, Lombard J. The potential utility of pharmacogenetic testing in psychiatry. *Psychiatry Journal*. 2014;2014:730956.

GENDEP Investigators; MARS Investigators; STAR*D Investigators. Common genetic variation and antidepressant efficacy in major depressive disorder: a meta-analysis of three genome-wide pharmacogenetic studies. *Am J Psychiatry*. 2013 Feb;170(2):207 – 17.

Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomics testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. *Pharmacogenomics J*. 2013 Oct;23(10):535 – 48.

Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatr*. 2010 May;15(5):473 – 500.

Kumar A, Datta SS, Wright SD, Furtado VA, Russell PS. Atypical antipsychotics for psychosis in adolescents. *Cochrane Db Syst Rev*. 2013 Oct 15;10:CD009582.

Mihaljević-Peles A, Bozina N, Sagud M. Pharmacogenetics in modern psychiatry. *Psychiat Danub*. 2007 Sep;19(3):231 – 3.

Mrazek DA. Psychiatric pharmacogenomic testing in clinical practice. *Dialogues Clin Neurosci*. 2010;12(1):69 – 76.

Mullins N, Perroud N, Uher R, et al. Genetic relationships between suicide attempts, suicidal ideation and major psychiatric disorders: a genome-wide association and polygenic scoring study. *Am J Med Genet B*. 2014 Jul;165B(5):428 – 37.

Niitsu T, Fabbri C, Bentini F, Serretti A. Pharmacogenetics in major depression: a comprehensive meta-analysis. *Prog Neuro-Psychoph*. 2013 Aug 1;45:183 – 94. doi: 10.1016/j.pnpbp.2013.05.011. Epub 2013 Jun 1. Erratum in: *Prog Neuro-Psychoph*. 2013 Dec 2;47:118 – 9.

Ramsey TL, Meltzer HY, Brock GN, et al. Evidence for a SULT4A1 haplotype correlating with baseline psychopathology and atypical antipsychotic response. *Pharmacogenomics*. 2011 Apr;12(4):471 – 80.

**Clinical trials:**
Searched clinical trials.gov on April 8, 2015 using terms pharmacogenomics and psychiatry.

Utility of PharmacoGenomics for Reducing Adverse Drug Effects (UPGRADE) NCT02081872; Companion Dx Reference Lab, LLC. Available at: https://clinicaltrials.gov/ct2/show/NCT02081872.

“UPGRADE aims to see whether data from Pharmacogenomic Testing (PGx) can help physicians manage patient medication regimens and assess if the testing has an effect on reducing adverse drug reactions, hospitalizations and emergency department visits.”

Impact of GeneSight Psychotropic on Response to Psychotropic Treatment in Outpatients Suffering From a Major Depressive Disorder (MDD) and Having Had an Inadequate Response to at Least One Psychotropic Medication Included in GeneSight Psychotropic (RCT) NCT02109939. University of Michigan and AssureRx Health Inc. Available at: https://clinicaltrials.gov/ct2/show/NCT02109939.

“Evaluate the impact of GeneSight Psychotropic on response to psychotropic treatment as judged by the mean change in the 17-item Hamilton Depression (HAM-D17) score from baseline to end of Week 8 of the study.”

**Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCDs):**
No NCDs identified as of the writing of this policy.

**Local coverage determinations (LCDs):**
No LCDs identified as of the writing of this policy.

**Commonly submitted codes**
Below are the most commonly used codes for the service(s)/item(s) subject to this policy clarification. This is not an exhaustive list of codes.

| CPT Code | Description |
|---|---|
| **81479** | Unlisted molecular pathology procedure |
| **81225** | CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17) |
| **81226** | CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN) |
| **81227** | CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6) |

cc: PerformCare Managers
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