HEALTH PLANS
UNIVERSITY OF UTAH

Medical Policy

Pharmacogenomic Testing for Behavioral Health Disorders

Related Policies:
Admin-020 Noncovered Behavioral Health-Related Services

Policy MP-030

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. Services requiring prior-authorization may not be covered, if prior-authorization is not obtained.
4. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

Description:

Mental illnesses are health conditions involving changes in thinking, emotion and behavior. Some common types are major depressive disorder, anxiety, schizophrenia, bipolar disorder, ADHD and Autism. In addition to counseling, treatment commonly involves one or more psychotropic medications aimed at alleviating symptoms. Although there are a wide variety of available and effective medications, treatment of mental health illnesses have relatively high rates of insufficient response. This often results in numerous trials of singular and combined medications to alleviate symptoms.

Pharmacogenomic studies examine how an individual's genetic inheritance affects the body's response to drugs. Different factors that may influence the variability of drug effects: age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genetic coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of molecules. Therefore, the choice of drug and dose are challenging, requiring close monitoring and adjustments, which prolongs the time to obtain optimal therapy. In some cases, serious adverse events may result.

It has been proposed that it may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway

(pharmacodynamics) of the drug and then predicting a potential response to specific medications in specific patients.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans does NOT cover genetic testing for the diagnosis and management of behavioral health disorders as they are considered investigational in all situations, including but not limited to the following:

A. To confirm a diagnosis of a behavioral health disorder in an individual with symptoms; or

B. To predict future risk of a behavioral health disorder in an asymptomatic individual; or

C. To inform the selection or dose of medications used to treat behavioral health disorders, including but not limited to the following medications:

   i. Selective serotonin reuptake inhibitors;

   ii. Selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors;

   iii. Tricyclic antidepressants or antipsychotic drugs.

U of U Health Plans does NOT cover genetic testing panels for behavioral health disorders as they are considered investigational for all indications, including but not limited to the following tests:

A. AIBioTech® "CardioloGene or PsychiaGene Genetic Panels, Pain Management, PersonaGene or Urologene Panels"

B. Genecept Assay "Genomind®"

C. SureGene Test for Antipsychotic and Antidepressant Response STA^{2}R test

D. GeneSight® "Analgesic, ADHD, or Psychotropic panel"

E. Proove® Opioid Risk assay or Drug Metabolism test panel

F. Mental Health DNA Insight panel

G. Millennium PGT^{SM}

H. INFINITI Neural Response Panel

I. IDgenetix-branded tests

2. **Medicaid Plans**
   Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at: https://medicaid.utah.gov/utah-medicaid-official-publications/ or the Utah Medicaid code Look-Up tool

   CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

Clinical Rationale

Much of the evidence on pharmacogenomics testing centers on the clinical validity of the testing being performed and the relevance of the genetic markers being tested as it relates to pharmacokinetics and pharmacodynamics. Along these lines, in 2017, Zhang et al. reviewed literature on the genetic basis of the variability among drug responses in genome-wide pharmacogenetic studies. Drug responses are highly variable because innumerable factors contribute to ultimate phenotypic outcomes. The genetic basis can be grouped into 3 categories; Monogenic (Mendelian) traits - inherited disorders and some severe adverse drug reactions, typically influenced by single rare coding variants; Predominantly oligogenic traits - variation largely influenced by a small number of genes, such as the interaction between the VKORC1 gene and CYP2C9; and Complex pharmacogenetic traits - most multifactorial quantitative traits, where a phenotype is influenced by numerous small-effect variants, together with epigenetic effects and environmental factors, they represent the largest category of pharmacogenetic possibilities. The authors found that the overall health benefits have not been established and based on the individual's whole-genome readout, genomic indicators of complex pharmacogenetic testing responses have unrealistic predictable power.

Little evidence has assessed clinical utility of this testing or economic utility. A 2018 Hayes report attempted to demonstrate the clinical utility of using pharmacogenomic testing to determine the choice and/or dosing of medications for individuals diagnosed with selected psychiatric and behavioral conditions, which included depression, mood disorders, psychosis, anxiety, attention-deficit/ hyperactivity disorder, or substance use disorder. No clinical evidence for any other conditions were found. The authors concluded that the extremely limited, very-low-quality and compromised evidence base did not demonstrate utility in improving health outcomes by changing patient management with the use of pharmacogenomic testing.

In 2019, Hayes also evaluated the use of *MTHFR* pharmacogenomic genotyping as a way to alter standard treatment in the choice and/or dosing of medications in order to improve diseased states and possible adverse events experienced by patients. *MTHFR* genetic variants have been proposed as pharmacogenetic markers for patients treated with second-generation antipsychotic drugs prescribed for the treatment in psychiatric disorders, such as schizophrenia. Several methods are currently available for the detection of *MTHFR* single nucleotide polymorphisms, primarily C677T and A1298C. Assays may be targeted and variant specific or may include *MTHFR* genotyping as part of a larger pharmacogenomic panel. The authors looked for clinical utility only and found a very low quality body of evidence available from articles that were relevant. Thus, determination of clinical utility with MTHFR genotyping for the treatment of psychiatric disorders has not been founded.

In addition, Hayes also published a report in September 2021 evaluating the analytical validity, clinical validity and clinical utility for the GeneSight® Psychotropic test for 15 genes which is a pharmaco-

genomic gene panel that evaluates gene-drug interactions using a combinatorial algorithm to help providers make medication decisions for patients with behavioral health conditions. The authors found no analytical or clinical validity studies and only 4 clinical utility studies. In which, the best available evidence included the GUIDED trial using an 8 gene version of the GeneSight Psychotropic 15 gene panel test. The primary outcome of the testing did not significantly improve symptoms, the subsequent post hoc reanalysis or subgroup analyses comparing results from the pharmacogenomics and treatment-as-usual (TAU) arms attained statistical significance; however, the impact of pharmacogenomics testing to help healthcare providers make informed medication decisions for patients with behavioral health conditions and ultimately improve patient outcomes remains unclear. The report concluded that there is an overall very low quality body of insufficient evidence to support the use of this test. Furthermore, none of the studies evaluated the currently marketed 15 gene version of the GeneSight Psychotropic test.

Several other small studies have been published related to clinical utility of this testing. A 2013 small double-blind randomized control trial (RCT) assessed the impact of using the GeneSight test, a five gene pharmacogenomic test with interpretive report, for the management of psychotropic medications used in major depressive disorder (Winner et. al.). Fifty-one subjects from an individual outpatient practice were enrolled in either standard treatment or medication guidance through GeneSight testing. All subjects underwent GeneSight testing, though results were not given to the physicians in the standardized treatment group until after study completion. At the 10-week follow-up, treating physicians dose-adjusted subjects' medication regimens with the same likelihood in the GeneSight group (53%) as the standardized treatment group (58%; p=0.66). However, patients in the GeneSight group who were initially on a medication classified as "use with caution and with more frequent monitoring" were more likely than those with the same classification in the unguided group to have a medication change or dose adjustment (100% vs 50% respectively; p=0.02). Depression outcomes, measured by the HAMD-17 score, did not differ significantly between groups at the 10-week follow-up. In conclusion, there were no significant differences in the depression outcomes, which were measured by the HAMD-17 score, between the groups at the 10 week follow-up. Economic utility was not assessed as part of this study.

In another study to evaluate the evidence to support pharmacogenetic biomarker testing guidance referenced in FDA drug labels, Wang et. al. (2014) used FDA databases and guidelines published by the Evaluation of Genomic Applications in Practice and Prevention Working Group to determine the clinical validity and utility of these recommendations. Of 119 notations in drug labels 36.1% provided evidence of clinical validity evidence while 15.1% provided evidence of clinical utility. Sixty-one labels (51.3%) made recommendations regarding clinical management based on the results of a biomarker test. Of these, 30.3% provided clinical utility data. A full description of supporting studies was included in 13 labels (10.9%). In conclusion, this study found that less than one-sixth of drug labels had convincing evidence referenced for clinical utility of biomarker testing, even though over half recommended biomarker tests for therapeutic decision making, therefore it seems premature to include biomarker testing recommendations on drug labels when there is no data to identify patient outcomes.

In 2017, Rosenblat et. al., and Health Quality Ontario conducted systematic reviews evaluating whether pharmacogenetics testing improves clinical outcomes for anxiety, major depressive disorder and other mood disorders or schizophrenia. Study quality was assessed using the Newcastle-Ottawa Scale in Rosenblat and the GRADE system in Health Quality Canada. The authors concluded that the studies were determined as low quality, because many were open-label, nonrandomized, industry-sponsored and their estimates were inaccurate. Neither review found improved patient outcomes or cost effectiveness by using guided treatment with genetic testing as opposed to standard of care.

A more recent systematic review conducted by Health Quality Ontario in 2021 evaluated six multi-gene pharmacogenomic tests that included decision-support tools to guide medication selection for major depression. This review also came to the conclusion that multi-gene pharmacogenomic tests may result in little or no difference in improvement in depression scores compared with treatment as usual, and that the impact on adverse events is uncertain. Economic utility for the management of major depression in people who had inadequate response to at least one medication was assessed and found that some of these tests maybe be cost-effective at the willingness-to-pay amount of $100,000 per QALY (quality of life year).

In a further attempt to identify clinical utility, Jung et. al. (2017), attempted to identify potential predictors of venlafaxine XR treatment outcomes in an organized genome-wide association study (GWAS) for Generalized Anxiety Disorder (GAD). Ninety-eight European American patients participated in a venlafaxine XR clinical trial for GAD, with Hamilton Anxiety Scale (HAM-A) response/remission at 24 weeks as the primary outcome measure. All participants were genotyped with the Illumina PsychChip, and 266,820 common single nucleotide polymorphisms (SNPs) were analyzed. Although no SNPs reached genome-wide significance, 8 SNPs were marginally associated with treatment response/ remission and HAM-A reduction at week 12 and 24 ($p<0.00001$). Some limitations of this study consisted of a small sample study, retroactive collection of DNA and no placebo arm in the first phase of the trial. In conclusion, although several identified genes may indicate markers crossing neuropsychiatric diagnostic categories, there were no significant genome-wide association results found.

Bradley et. al., (2018) conducted an industry-funded trial that randomized 685 patients, between the ages of 19 and 87, with depression and/or anxiety disorders, equally into groups whose treatment was guided by either NeuroIDgenetix or standard of care. Outcomes included HAMD and the Hamilton Rating Scale for Anxiety (HAMA) and adverse drug events. Depression and anxiety symptom data were collected at 4-, 8-, and 12-week follow-up visits, using HAM-A and HAM-D17 interviews. Medication changes and prescription use was tracked at all visits. Only patients with moderate or severe disorders (HAM scores 18 and above) were included in the efficacy analysis. The rate of adverse drug events were very low and did not differ statistically between groups.

In 2018 Zeier et. al., examined the evidence base for several commercial combinatorial pharmacogenetic testing products whose potential utility is to identify gene-drug interactions that effect the treatment response to antidepressant medications. The authors mention available literature is noted to have publication bias, as the studies are conducted by persons with significant financial interests and therefore questions the scientific integrity. In conclusion, even though some of the preliminary data sounds promising, at this time there is insufficient evidence to determine whether combined pharmacogenetic testing provides valid information and improves the efficacy, tolerability or affordability of specific pharmacotherapies and works well in real-life practice.

Hayes published an updated clinical utility evaluation of pharmacogenomic testing in December 2021 to inform the selection or dose of medications for individuals diagnosed with depression, anxiety disorder, bipolar disorder, schizophrenia spectrum or other psychotic disorders. The review noted evidence from 9 controlled clinical trials comparing medication treatment of mental health disorders guided by pharmacogenomic testing reported inconsistent results across studies. Three of 6 trials that primarily enrolled patients with depressive disorders reported statistically significant results for the primary endpoint. Three post hoc analyses of selected original trial data reported statistically significant results whereas the original results did not. There were insufficient studies available to assess outcomes for bipolar and schizophrenia spectrum disorders. Genetics account for only a portion of variability in medication response; environment, patient comorbidities, as well as individual physiological and psychological factors may also contribute to treatment response. Therefore, trials focused solely on

pharmacogenomic testing may fail to consistently provide evidence regarding the clinical utility to inform the selection or dose of medications to improve clinical outcomes. The authors found that the overall quality of evidence is considered fair for study design; however, due to the lack of results consistency, pharmacogenomic-guided treatment of mental health disorders to improve health outcomes remains uncertain.

Further, the FDA released a Safety Communication in 2018 cautioning the use of unproven genetic tests that allege to predict a patient's response to specific medications by using DNA variations for conditions such as depression. There may not be enough scientific or clinical evidence to support these claims, especially if they are not FDA approved. According to the communication plan, "the FDA is aware of genetic tests that claim results can be used to help physicians identify which antidepressant medication would have increased effectiveness or side effects compared to other antidepressant medications. However, the relationship between DNA variations and the effectiveness of antidepressant medication has never been established." Furthermore, making changes to a patients medication regimen based on these tests results could cause "potentially serious health consequences".

Several societies have also released statements regarding pharmacogenomics testing for behavioral health conditions. The International Society of Psychiatric Genetics (ISPG) created a Residency Education Committee in 2018 to identify and recommend key genetic knowledge that should be taught in psychiatric training programs. Genetic testing is only recommended by the committee as part of a diagnostic workup for patients with autism spectrum disorders or intellectual disability. As to pharmacogenetic testing, the committee states that even though there is commercial testing widely available, the utility has not yet been established, therefore it is not recommended.

These recommendations by the ISPG were updated in 2021 by expert consensus, which concluded that to inform medication selection and dosing of several commonly-used antidepressant and antipsychotic medications, current published evidence, prescribing guidelines, and product labels support the use of pharmacogenetic testing for two cytochrome P450 genes (CYP2D6, CYP2C19). In addition, the evidence supports testing for human leukocyte antigen genes when using the mood stabilizers carbamazepine (HLA-A and HLA-B), oxcarbazepine (HLA-B), and phenytoin (CYP2C9, HLA-B). For valproate, screening for variants in certain genes (POLG, OTC, CSP1) is recommended when a mitochondrial disorder or a urea cycle disorder is suspected. The review acknowledges that there is disagreement about the role of pharmacogenetic testing in antidepressant prescribing, and that clinical efficacy was only evaluated in limited populations, while cost-effectiveness was examined in industry-sponsored studies.

In April of 2019, the American Association for Clinical Chemistry (AACC) brought together an international panel of more than 50 experts to thoroughly look at the 2014 guidelines from the ISPG. Although genotypes from large numbers of common variants may be combined to demonstrate an overall genetic risk score, clinical value has not yet been established. Overall, the panel determined that more education and research is needed to provide clarity on genetic testing's role in psychiatric care.

Applicable Coding

CPT Codes

Non-Covered Codes

0029U Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)

0032U	COMT (catechol-O-methyltransferase) (drug metabolism) gene analysis, c.472G>A (rs4680) variant
0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
0078U	Pain management (opioid-use disorder) genotyping panel, 16 common variants (i.e., ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder
0173U	Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 14 genes
0175U	Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes
0345U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
0392U	Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug
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)
81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22)
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *7)
81291	MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81401	Molecular pathology procedure level 2
81479	Unlisted molecular pathology procedure

HCPCS Codes

No applicable codes

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