PHARMACOGENETIC TESTING

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Related Commercial Policies
- Cardiovascular Disease Risk Tests
- Chemosensitivity and Chemoresistance Assays in Cancer

Community Plan Policy
- Pharmacogenetic Testing

Medicare Advantage Coverage Summaries
- Genetic Testing
- Laboratory Tests and Services

COVERAGE RATIONALE

The use of pharmacogenetic Multi-Gene Panels to guide therapy decisions is proven and medically necessary for antidepressants and antipsychotics medication when ALL of the following criteria are met:
- The individual has a diagnosis of major depressive disorder or anxiety; **and**
- The individual has failed at least one prior medication to treat their condition; **and**
- The Multi-Gene Panel has no more than 15 relevant genes (refer to Table 1).

The use of pharmacogenetic Multi-Gene Panels for genetic polymorphisms for any other indication, including but not limited to pain management, cardiovascular drugs, anthracyclines, or polypharmacy, is unproven and not medically necessary for evaluating drug-metabolizer status due to insufficient evidence of efficacy.
Examples of these Panels include, but are not limited to the following:
- GeneSight® Analgesic
- GeneSight® ADHD
- SureGene Test
- Pain Medication DNA Insights®
- PharmacoDx

DEFINITIONS

Multi-Gene Panel: Genetic tests that use next-generation sequencing to test multiple genes simultaneously. Also called Multi-Gene test, multiple-gene Panel test and multiple-gene test (National Cancer Institute Dictionary of Genetics).

Panel: A group of laboratory tests that are performed together to assess a body function or disease (Medicare, 2019 and McGraw Hill, 2002).

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

CPT Code	Description
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*)
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
81479	Unlisted molecular pathology procedure

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DESCRIPTION OF SERVICES

Pharmacogenetics encompasses variation in genes that encode drug-metabolizing enzymes, drug transporters, and drug targets, as well as other specific genes related to the action of drugs. A slight variation in the deoxyribonucleic acid (DNA) sequence can result in a subtle change in a protein which translates into major differences in how the protein functions. The study of variations in DNA sequence as related to drug response is referred to as pharmacogenetics, and pharmacogenetic testing involves genotyping to detect relevant variants. Genetic variations can be associated with suboptimal drug response, for example poor efficacy or adverse events.

A pharmacogenetic test is meant to guide treatment strategies, patient evaluations and decisions based on its ability to predict response to treatment in particular clinical contexts. An overview of many aspects of pharmacogenetics and its application in specific clinical settings is provided by the National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines (2010). When testing is targeted to evaluate an individual's response to a specific drug, typically only one gene is analyzed. For warfarin, also known as coumadin, two to three genes are tested. However, laboratories have developed Multi-Gene Panels that include more than two genes in order to proactively evaluate an individual's possible response to many drugs. This policy is designed to address Multi-Gene panel testing.

CLINICAL EVIDENCE

Anxiety and Depression

The Pharmacogenomics Knowledge for Personalized Medicine database (PharmGKB) is a NIH-funded resource that provides information about how human genetic variation affects response to medications, and provides a centralized resource of international gene-drug professional society prescribing guidelines, FDA label information on gene-drug recommendations, and evidence based clinical curations (Whirl-Carillo et al., 2012).

Table 1 lists genes that can inform antidepressants and antipsychotics that are found in PharmGKB with an evidence level of 2B (moderate evidence of an association) or better (PharmGKB, 2019a and 2019b).

Table 1. Antidepressant, Antipsychotic Drugs and Associated Genes

Drug	Gene(s)	Select Associated References
Sertraline	*CYP2C19, CYP2D6, COMT, TXNRD2*	CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)
Citalopram	*CYP2C19, SLC6A4, GRIK4, HTR2A, FKBP5, COMT, TXNRD2*	• CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015) • Polymorphisms in *GRIK4, HTR2A*, and *FKBP5* Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010)
Escitalopram	*CYP2C19, SLC6A4, COMT, TXNRD2*	• CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015) • Interaction between serotonin transporter gene variants and life events predicts response to antidepressants in the GENDEP project (Keers et al., 2011)
Fluoxetine	*FKBP5, COMT, TXNRD2*	Polymorphisms in *GRIK4, HTR2A*, and *FKBP5* Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010)
Paroxetine	*CYP2D6, HTR1A, FKBP5, COMT, TXNRD2*	• CPIC Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015) • Polymorphisms in *GRIK4, HTR2*A, and *FKBP5* Show Interactive

Drug	Gene(s)	Select Associated References
		Effects in Predicting Remission to Antidepressant Treatment (Horstmann, et al., 2010) • SSRI response and HTR1A (Yevtushenko et al., 2010)
Fluvoxamine	CYP2D6, COMT, TXNRD2	CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)
Venlafaxine	CYP2D6, FKBP5	Polymorphisms in GRIK4, HTR2A, and FKBP5 Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010)
Amitriptyline	CYP2C19, 2D6	CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017)
Nortriptyline	CYP2D6	CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017)
Clomipramine	CYP2C19, 2D6	CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)
Doxepin	CYP2C19, 2D6	CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017)
Imipramine	CYP2C19, 2D6	CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017)
Olanzapine	ANKK1, DRD2, MCR4, HTR2C	• Genetic variation and the D2 dopamine receptor: implications for the treatment of neuropsychiatric disease (Mickey et al., 2016) • Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis (Zhang et al., 2016)
Clozapine	ANKK1, DRD2, MCR4, HTR2C	• Genetic variation and the D2 dopamine receptor: implications for the treatment of neuropsychiatric disease (Mickey et al.,2016) • The combined effect of CYP2D6 and DRD2 Taq1A polymorphisms on the antipsychotics daily doses and hospital stay duration in schizophrenia inpatients (Kurylev et al., 2018) • Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis (Zhang et al., 2016)
Risperidone	CYP2D6, ANKK1, DRD2, MCR4, HTR2C	• DPWG Guideline for risperidone and CYP2D6 (Swen et al., 2011) • Genetic variation and the D2 dopamine receptor: implications for the treatment of neuropsychiatric disease (Mickey et al., 2016) • Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis (Zhang et al., 2016)
Mirtazapine	CYP2D6, FKBP5	• Multicenter study on the clinical effectiveness, pharmacokinetics, and pharmacogenetics of mirtazapine in depression (Jaquenoud Sirot et al., 2012) • Polymorphisms in GRIK4, HTR2A, and FKBP5 Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010)
Desipramine	CYP2D6	CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017)
Trimipramine	CYP2C19, 2D6	CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017)

Up to 42% of variance in therapy response for major depressive disorders (MDD) can be explained by genetic variation, which has led to the development of pharmacogenetic tests to inform the use of certain psychiatric medications. Prospective randomized clinical trials have been performed to validate the clinical validity and utility of a number of pharmacogenetics (PGx) multi-gene panels.

Bousman et al. (2019) conducted a systematic review of the literature and meta-analysis of prospective, randomized controlled (RCT) trials on the use of PGx multi-gene panels that had included a decision support tool to guide clinicians in the use of the results for MDD. RCTs were evaluated using the Cochrane criteria. A total of five RCTs representing 1737 patients were identified. Individuals receiving PGx testing with physicians utilizing a guided decision support tool

(n=887) were 1.17 times more likely (p=.005) than the treatment as usual (TAU) group (n=850) to report symptom remission. Similarly, Rosenblat et al. (2018) conducted a meta-analysis on the use of PGx multi-gene panels to guide treatment of MDD. Article databases were searched up to December 2017 on the human clinical utility of pharmacogenetics for the treatment of MDD. Four randomized clinical trials and two open-label controlled cohort studies were included. The outcomes analyzed were response and remission between PGx and TAU groups. The pooled risk ratio for overall treatment response was 1.36 in favor of PGx guided treatment compared to TAU, and 1.74 for PGx for remission when compare to TAU. The studies were heterogeneous across population, criteria, and PGx testing used.

Menchon et al. (2019) examined the influence of patient characteristics such as age, baseline severity, and duration of episode on the clinical utility of PGx testing for psychiatric drugs from the AB-GEN study, a randomized 12-week long study comparing TAU toPGx guided therapy selection in 280 adults with MDD. The primary outcomes analyzed were the Patient Global Impression of Improvement (PGI-I) scale and the Hamilton Depression Rating Scale (HAM-D17). Patients generally showed no difference in sustained response at the 12-week end point between the TAU and PGx group (Perez, et al., 2017). However, the PGx group had a higher response rate than TAU, and when subjects were removed whose physicians did not follow the genetic testing recommendations, the response rate improved further. Side effects were less in the PGx group by 6 weeks, and this was maintained at week 12. The primary dependent variable identified was the number of previously failed medication trials. In the Menchon et al. (2019) reanalysis by patient demographics, additional important variables were identified. Age was important as PGx testing significantly improved outcomes in those under age 60, but not over age 60. Outcomes were also improved in those with moderate to severe depression, but not those with mild depression. Genetic testing improved PGI-I in one year or less from diagnosis, but not HAM-D17. The effect on HAM-D17 was not significant until the cutoff from time of diagnosis was increased to 5 years. After this, however, a null effect was seen, and individuals who were more than 5 years from their diagnosis were actually worse off in the PGx arm than TAU. To determine which type of patient is most likely to benefit from pharmacogenetic testing for psychiatric therapies, more prospective, randomized trials are needed.

GUIDED is a 24 week RCT conducted between April 2014 and February 2017 comparing active treatment groups guided by PGx information, to active treatment groups receiving usual care (TAU) for MDD (Greden et al., 2019). Sixty sites participated, and patients were referred to the study when it was self- or clinician reported to have inadequate response to at least one antidepressant. The average number of medications failed in the cohort was three, making this a difficult to treat population. Genotyping was for eight genes, *CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A,* and *SLC6A4* and results were evaluated and reported using a proprietary pharmacogenetic algorithm from Assurex Health. Participants were blinded to the study arm but clinicians were not, since they needed to consult the PGx results to guide treatment. Using the results to guide treatment was not mandated. Patients were assessed at 4, 8, 12 and 24 weeks using the HAM-D17, which was administered by blinded raters. A total of 1167 enrolled patients made it through week 8 with 607 in TAU and 560 in PGx guided. HAM-D17 scores decreased in the TAU arm by 24% and in the PGx arm by 27%, but the difference was not statistically significant. Treatment response, defined as ≥50% decrease in depression, was greater in the PGx arm (26%) than TAU (20%). The depression remission rate, defined as score of ≤7 for HAM-D17, was 10% with TAW and 15% with PGx (p=.007). Additionally, at week 8, there was no difference between the groups in reported side effects. When patients taking incongruent medications were evaluated as a separate cohort, those who switched to congruent medications by week 8 experienced significantly fewer side effects. Medication prescriptions that aligned with PGx results at baseline were 77% in the TAU group and 79% in the PGx group. By week 8, the PGx group increased to 91%, and the TAU group was unchanged. After 8 weeks, clinicians in the TAU arm were unblinded and could use the PGx results if they chose. A total of 913 participants completed through week 24 with 456 in TAU and 457 in the PGx guided arm. Overall, in the PGx group, HAM-D17 scores decreased by 43% at week 24 relative to baseline. Response and remission increased by 70% and 100%, respectively, from week 8 to week 24. While the primary outcome being analyzed, symptom improvement at week 8, was not different between the two groups, there was significant difference in response and remission in the PGx group on other measures.

A panel of ten genes with select polymorphisms combined with a proprietary algorithm, the NeuroIDgenetix® Test, was the subject of a RCT to evaluate clinical utility for guiding treatment for depression and anxiety (Bradley et al., 2018). Genes included *CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, COMT, HTR2A,* and *MTHFR.* Participants were identified from 20 independent clinical sites in the US that represented psychiatry, internal medicine, family medicine, and obstetrics and gynecology. A total of 685 patients were included in the study, ranging in age from 19 to 87, and all had a diagnosis of depression or anxiety using the DSM-V criteria and verified by the MINI Psychiatric Interview. Most were female (73%) with diagnoses of depression (n=246), anxiety (n=235) or both (n=204) Participants were either 'New to Treatment' (newly diagnosed or taking medications for less than 6 weeks) or 'Inadequately Controlled' with medications as defined by lack of efficacy or treatment discontinuation due to adverse events or intolerability; although the authors did not report the distribution. PGx testing was performed in all subjects but was only shared with the physicians of those in the PGx arm. Patients were assessed at 4, 8 and 12 weeks using the HAM-D17 and the Hamilton Rating Scale for Anxiety (HAM-A), with their physicians blinded to the results. Adverse

events were captured via the Adverse Drug Event form developed by external psychiatric consultants, and a blinded clinician ranked the adverse events on a severity scale. The PGx testing group showed a greater response and remission rate with odds ratios of 4.72 and 3.54 respectively, than the TAU group at 12 weeks. In the anxiety group, those that received testing had a higher response rate at 8 and 12 weeks with an odds ratio of 1.76, compared to the TAU group. Physicians made at least one medication change in 81% of those receiving testing than the control group (64%) at the two-week time point when results were returned to physicians. No difference was found in adverse drug events between the two treatment groups. In a post-hoc analysis on the 'Inadequately Controlled' cohort remission rates (42% vs. 27%, p =0.03) and response rates (62% vs. 44%, p=0.01) response rates were greater with PGx than TAU.

Jung et al. (2017) conducted a genome-wide association study (GWAS) in Generalized Anxiety Disorder (GAD) to identify potential predictors of venlafaxine XR treatment outcome. 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, eight SNPs were marginally associated with treatment response/remission and HAM-A reduction at week 12 and 24 (p<0.00001). The authors concluded that several identified genes may indicate markers crossing neuropsychiatric diagnostic categories. The authors acknowledged that the limitations of this study include small sample size and the lack of statistical power for a GWAS. Areas for future research include the replication of results with larger samples sizes to increase statistical power and further elucidate the treatment effects of antidepressant venlafaxine XR on GAD.

Researchers enrolled 528 (outpatients and inpatients) from 18 hospitals and associated mental health centers in Spain from July 2014 to June 2015 in the AB-GEN study, a 12-week, double-blind, parallel, multi-center RCT to evaluate the effectiveness of PGx testing for drug therapy guidance for MDD. Patients with a CGI-S ≥ 4 and requiring antidepressant medication de novo or changes in their medication were randomized to a PGx or TAU group. PGx testing was conducted by Neuropharmagen, and results were reported using their web-based clinical decision support tool. Thirty genes and relevant single nucleotide polymorphisms were analyzed. The primary endpoint was measuring a sustained response on the Patient Global Impression of Improvement (PGI-I) of ≤ 2 within the 12-week follow-up. Follow up was conducted by phone, and the interviewer was blinded to the participant's study arm. A patient was considered to have a sustained response with a PGI-I score of 2 or less if they reported their condition to be "much better" or "very much better." Only 280 of 528 patients completed the study. A difference in sustained response was not observed between PGx and TAU at 12 weeks. Overall the PGx group had a much higher response rate, and this improved when removing the patients whose physicians did not follow the PGx recommendations. Effects were greatest in patients who had failed up to three prior medications. Of those who reported side effects at baseline, the PGx group was more likely to report fewer side effects than the TAU group (Perez et al., 2017). This study is interesting as it uses real world practices and clinicians, a heterogeneous population with variable disease states and prior treatment failures, and clinicians could choose to not follow the PGx recommendations. Additional studies are needed to replicate these findings across larger, ethnically diverse study groups.

Perlis et al. (2017) reported on a propensity-score matched case-control analysis of health claims data from a US payer that examined the longitudinal claims of individuals with a mood or anxiety disorder. Claims from individuals who had received the Genecept pharmacogenetic ten gene test from Genomind were compared to case-matched controls who matched on gender, age, and diagnosis who did not receive testing. Diagnoses that were included were depressive disorders, any anxiety diagnosis, bipolar disorder, and any substance abuse diagnosis. Co-morbidities that were accounted for in the analysis included hyperlipidemia, low back pain, hypertension, migraine and other headaches, diabetes mellitus, and any mental health visit. Of the 1639 individuals who received genetic testing, it was possible to match 817. Patients who had PGx testing had 40% fewer emergency room visit for any cause and 58% fewer hospitalizations for any cause. There was no difference between the groups in the number of psychiatric medications prescribed, or mood disorder related inpatient hospitalizations. Selection bias, since this was an observational study, was a physician that ordered genetic testing might, in theory, be more aggressive in patient management. The study's authors concluded that randomized prospective clinical trials are needed to further validate the clinical utility of genetic testing for psychiatric disorders.

Cardiovascular Disease

The real world clinical utility of pharmacogenetic testing for managing cardiovascular disease was studied by Billings et al. (2018). A retrospective cohort of individuals was identified through pharmaceutical, medical and laboratory claims data from a national health insurer from January 2011 through September 2015. Baseline data and outcomes were measured over a 12-month period. Individuals who received PGx testing that included *CYP2C19, CYP2C9, VKORC1, F5, F2,* and *MTHFR* were matched to controls based on demographics and diagnoses. Pharmacogenetic testing was ordered at the physician's discretion, and was not influenced by the study. The total number of individuals tested was 11,060 and 178,096 matched controls were identified. Outcomes evaluated through claims data included pharmacy costs, medical costs, emergency room visits, outpatient visits, emergency room stays, controlling for demographics, coverage type, low income, cardiovascular disease and other co-morbidities, such as diabetes. The PGx

test group appeared significantly more likely to experience stroke, pulmonary embolism, deep vein thrombosis, or a composite event than the control group. Real world pharmacogenetic testing did not appear to improve outcomes based on claims analysis.

Anthracyclines

PharmGKB curators (PharmGKB) found evidence of 2B (moderate evidence) or better with the following genes and clinical impact related to anthracyclines; *NQO1, GSTP1, PNPLA3, SLC28A3, HAS3, SLC28A3, CBR3,* and *CYP19A1.* In addition, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) (Aminkeng et al., 2016) found additional strong clinical evidence for *RARG* and *UGT1A6*.

Anthracyclines are an important category of chemotherapeutic agents for hematological and solid tumors, but are associated with a high rate of anthracycline associated cardiotoxicity (ACT) that can result in symptoms during therapy or even years after therapy is completed. Sagi et al. (2018) conducted genotyping of 26 genes and 70 single nucleotide polymorphisms (SNPs) associated with anthracycline metabolism and retrospective review of medical records of 622 pediatric acute lymphoblastic leukemia (ALL) and 39 osteosarcoma (OSC) patients treated between 1989 and 2015 in Hungarian pediatric oncology centers. Patients with comorbidities such as Down syndrome or prior cardiac findings were excluded. Blood samples were taken on ALL patients in remission. All patients were followed by echocardiography routinely during and after treatment, and retrospective chart review examined the following categories; at baseline (used as a control), in the acute phase, during oral maintenance, at the end of treatment, 2-3 post diagnosis, 5-10 years after diagnosis, and 10-15 years post diagnosis. SNPs in *ABCC2, NQO1, SLC22A6,* and *SLC28A3* were associated with decreased fractional shortening and ejection fraction, particularly in the 5-10-year period after diagnosis. *NQO1* SNP rs1043470 T was associated with lower left ventricular function in the acute phase and 5-10 years post diagnosis. *CYP3A5* rs4646450 TT was found in 17% of ALL individuals with anthracycline associated cardiotoxicity (ACT) with a fractional shortening less than 28, and appeared to be more prominent in ACT overall, particularly in boys and the ALL group. Additional studies are needed that are prospective with long term follow up to further understand how pharmacogenetic testing can contribute to understanding ACT.

NCCN Guidelines for Pediatric ALL recommend testing TPMT and NUDT15 prior to or in the setting of excessive toxicity with thiopurine therapy but do not include any recommendations for pharmacogenomics testing prior to anthracyclines (NCCN, 2019).

Pain Management

Muriel et al. (2019) conducted a six month, observational, prospective study on the use of pharmacogenetic testing for 88 patients involved in long term opioid deprescription treatment of non-cancer related pain in the Pain Unit of Alicante General Hospital in Spain. Visits were monitored and analyzed based on various genotypes. Visits included baseline, follow-up and final, and other parameters tracked were opioid rotation or discontinuation, adverse drug events and suspected adverse drug reactions (ADRs). Genotyping consisted of the following genes and variants using RT-PCR: *OPRM1* (A118G), *ABCB1* (C3435T), *COMT* (G472A), *OPRD1* (T921C) and *ARRB2* (C8622T). Five patients were lost to follow up. The remaining participants were 64% female and 100% Caucasian. In the baseline visit, a median of 6 adverse events were recorded including dry mouth, constipation, sleep disruption, and depression. There was no difference recorded in ADRs from baseline through final visits. A total of 1659 ADRs were reported in 359 visits for this cohort, and the most common by system classification were psychiatric (21%) and gastrointestinal (20%). At the baseline visit, ADRs varied between *OPRM1* genotypes, with individuals who were AA at that A118G locus having, on average, two or more ADRs than AG/GG patients. Nausea and other gastrointestinal ADRs followed this same pattern. *COMT* genotyping was similar; with AA/GG patients have more ADRs, and those that were *COMT* AG less likely to have loss of libido, skin redness, vomiting, or sexual dysfunction. The *OPRD*-CT genotype also showed less association with sexual dysfunction and reproductive system disorders. The authors were surprised that the number of ADRs did not change over the course of the study, and they also noted that the use of antidepressants increased from the beginning to end of the study. Antidepressants can have similar ADRs to opioids, so this may be a confounding variable. The authors found value in the PGx testing as a predictor of who may experience nausea and gastrointestinal discomfort, and highlights the potential promising use of PGx in opioid management.

General Pharmacogenetic Multi-gene Panel Testing

Medication management is a critical service for polypharmacy patients. Kim et al. (2018) conducted an observational study of Medication Management Therapy (MTM) patients and the role of pharmacogenetic testing on a cohort of patients identified in the Magellan Health database. Inclusion criteria included being eligible for MTM services, taking six of more chronic medications for three or more chronic conditions, and incurring Medicare-mandated medication costs in the quarter prior to enrollment. The study consisted of one standard treatment as usual MTM arm, which is counseling by a pharmacist by phone, an intervention arm of MTM plus a clinical decision support tool to aid in managing polypharmacy (CDST), and an intervention arm that added PGx testing to MTM and CDST. PGx testing included the genes *CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP3A5,* and *VKORC1* and was performed at Genelex. After the initial MTM call, pharmacists would collect demographic information, active medications, and a history of adverse drug events. After the MTM group exceeded 100 patients, patients were assigned to either the CDST arm or the PGx

arm based on whether or not their birth year was odd (PGx) or even (CDST). Patients who were assigned to the PGx arm were contacted by phone by the MTM counselor with instructions and a buccal swab kit was mailed. There were 104 in the MTM arm, 103 to the CDST arm, and 135 to PGx. However, 77 patients failed to return the buccal swab and were reassigned to the CDST arm, so only 58 patients were available for the PGx arm. On average, patients were 77 years old and took 11 medications. The baseline therapeutic indications were similar across all arms, and on average three drug therapy problems (DTP) were identified per participant. Blinded clinical pharmacists ranked the DTPs and considered the seriousness in 31% of PGx patients compared to only 4.9% of non-PGx patients. The more serious a DTP was considered, the more likely it was a prescriber would accept therapy change recommendations, particularly in the PGx group, where the odds ratio for accepting a change was 2.39, compared to 1.95 in the other groups. The authors concluded that MTM enhanced with a CDST or PGx did not improve the number of DTPs identified, but both helped pharmacists identify DTPs better, and PGx testing made recommendations more acceptable to the ordering clinician. More studies are needed to demonstrate the clinical utility of general PGx testing in patients with polypharmacy.

Borobia et al. (2018) reported on the implementation of a PGx program in 2014 at La Paz University Hospital (LPUH) in Madrid. LPUH is a 1,308-bed tertiary-care teaching hospital of the Spanish NHS serving a population of ~600,000 people. The goal of the study was to implement PGx into clinical practice and evolve from an *ad* hoc strategy linked to a prescription to a proactive practice, where genetic information would be obtained prior to a prescription in at risk populations. The targeted populations were at risk for inflammatory bowel disease, psoriasis, transplant patients, high cardiovascular disease risk, leukemia, and colorectal cancer. The authors utilized a 180 SNP panel (PharmArray) for testing. Ordering providers would submit a recommendation and request for testing to a centralized Pharmacogenetic Testing Unit who would evaluate the request based on patient demographics, if the requested marker fell into one of three categories. Category A was for pre-emptive screening of an actionable marker, such as HLA-B5701 for abacavir response. Category B was for drugs with a well-defined protocol for treating certain diseases, such as TPMT for thiopurine response for treatment of inflammatory bowel disease. Category C was for drugs without a well-defined protocol. In this situation, the pharmacogenetics unit would evaluate the therapeutic issue and determine if a pharmacogenetic test would be clinically useful. From January 2014 through December 2016, the Pharmacogenetic Testing Unit received 2,539 consultation requests. The most common tests were TPMT and MTHFR. There were 1,939 requests for treatment selection that had well defined protocols and 711 for drugs with pharmacogenetic treatment recommendations for certain diseases, or had poorly defined recommendations. Of these, 600 were found appropriate and approved, and 32% had a molecular profile that impacted the drug. In this sub-group, 58% (107) had a dose adjustment as a result. The total cost of the program was estimated at 216 € ($254) per patient, and 91% of physicians surveyed said they would now use pharmacogenetics regularly.

O'Donnell et al. (2014, 2017) implemented a PGx testing program, The 1200 Patients Project, at the University of Chicago to adult patients who were regularly taking at least one prescription drug, but not more than six. Patients could be referred by a care provider or self-referred to the program. After participating in an informed consent process, patients were tested for PGx variants using a commercially available multi-gene pharmacogenetic testing panel (Sequenom ADME). Overall, 868 patients that completed PGx testing had 2279 patient encounters that were reviewed. Four medical specialties and seventeen providers represented all clinic visits; executive health, nephrology, hepatology, and pulmonology. The most prevalent medications included aspirin, atorvastatin, hydrochlorthiazide, lisinopril, and amliodipine. Of all medications on active patient drug lists, 34% had associated alerts (n=2869) that included green (21%), cautionary yellow (13%) and high risk red (0.5%). The remaining medications had no actionable pharmacogenetic information. Of the 2869 alerts provided, green alerts were viewed 40% of the time, and 4% had medication changes documented. Yellow alerts were viewed 66% of the time, and 5% had medication changes documented. Red alerts were viewed 89% of the time, and 24% had medication changes documented. Nearly half of all medication changes were for omeprazole and atorvastatin. Simvastatin and rabeprazole had the highest overall percentage of changes influenced by the PGx test results. The authors note that limitations to this study include the small number of providers involved and the modest response to actionable alerts, with only 60 medication changes out of 405 possibly actionable red and yellow alerts. In addition, the providers included in the study were also co-investigators which may highlight a bias toward pharmacogenetics, and they knew their behavior was being examined, which may have altered their choices from what they would have done if they had not known their choices were being monitored.

Professional Societies
National Academy for Clinical Biochemistry (NACB)
According to the NACB (2010), pharmacogenetic testing is not currently recommended for general population screening.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at:

https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm.
(Accessed June 11, 2019)

Medicare does not have a National Coverage Determination (NCD) that specifically addresses the use of multigene pharmacogenetic panels to guide therapy decisions for prescribing antipsychotics, antidepressants and anthracyclines. Local Coverage Determinations (LCDs) exist; refer to the LCDs for MolDX: Molecular Diagnostic Tests (MDT), CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing, Biomarkers Overview, MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing and Molecular Diagnostic Tests (MDT).

Medicare does not have an NCD that specifically addresses the use of multigene pharmacogenetic panels that determine opioid-use disorder. However, LCDs exist for CPT code 0078U; see the LCDs for MolDX: Molecular Diagnostic Tests (MDT). (Accessed June 14, 2019)

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Date	Action/Description

10/01/2019	**Coverage Rationale**
	• Added language to indicate the use of pharmacogenetic Multi-Gene Panels to guide therapy decisions is proven and medically necessary for antidepressants and antipsychotics medication when all of the following criteria is met:
	 ○ The individual has a diagnosis of major depressive disorder or anxiety; and
	 ○ The individual has failed at least one prior medication to treat their condition; and
	 ○ The Multi-Gene Panel has no more than 15 relevant genes
	• Replaced language indicating "the use of pharmacogenetic Multi-Gene Panels for genetic polymorphisms is unproven and not medically necessary for evaluating drug-metabolizer status" with "the use of pharmacogenetic Multi-Gene Panels for genetic polymorphisms *for any other indication [not listed as proven and medically necessary], including but not limited to pain management, cardiovascular drugs, anthracyclines, or polypharmacy,* is unproven and not medically necessary for evaluating drug-metabolizer status"
	• Revised list of examples of unproven and not medically necessary Panels:
	 ○ Added:
	  ▪ Pain Medication DNA Insights®
	  ▪ PharmacoDx
	 ○ Removed:
	  ▪ AIBioTech® CardioloGene Genetic Panel
	  ▪ AIBioTech® Pain Management Panel
	  ▪ AIBioTech® PsychiaGene Genetic Panel
	  ▪ AIBioTech® Urologene Panel
	  ▪ AIBioTech® PersonaGene Panel
	  ▪ Genecept™ Assay
	  ▪ GeneSight® Psychotropic
	  ▪ Millennium PGT^{SM} Millennium PGT[SM]
	  ▪ Proove® Drug Metabolism test panel
	  ▪ Proove® Narcotic Risk test panel
	 ○ Replaced "SureGene Test *for Antipsychotic and Antidepressant Response (STA^{2}R)*" with "SureGene Test"
	Definitions
	• Added definition of:
	 ○ Multi-Gene Panel
	 ○ Panel
	Supporting Information
	• Updated *Description of Services*, *Clinical Evidence*, *CMS*, and *References* sections to reflect the most current information
	• Archived previous policy version 2019T0587D

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.