Pharmacogenetic Panel Testing (for Louisiana Only)

Policy Number: CS149LA.~~C~~H
Effective Date: ~~October1, 2022~~TBD

➲ Instructions for Use

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Application

This Medical Policy only applies to the state of Louisiana.

Coverage Rationale

State-Specific Criteria

The coverage criteria for genetic counseling contained in this policy represents Louisiana Medicaid Managed Care Organization Manual (LA MCO) coverage policy and is set forth below in accordance with State requirements.

Genetic Counseling

Genetic counseling before and after all genetic testing is required. Counseling must consist of at least all of the following and be documented in the medical record:

- **Obtaining a structured family genetic history**
- **Genetic risk assessment; and**
- **Counseling of the enrollee and family about diagnosis, prognosis, and treatment (LA MCO Genetic Counseling and Testing, page 112)**

Additional Non State Criteria

The use of pharmacogenetic Multi-Gene Panels (5 or more genes) to guide therapy decisions is proven and medically necessary for antidepressant and antipsychotic medications~~antidepressants and antipsychotics medication~~ when all ~~of~~ the following criteria are met:

- The individual has a diagnosis of major depressive disorder or **generalized** anxiety **disorder**; **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 (5 or more genes) 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 ~~P~~**p**anels~~Panels~~ include, but are not limited to the following:

- GeneSight® Analgesic
- GeneSight® ADHD
- Pain Medication DNA Insights®
- PharmacoDx
- SureGene Test

The use of the PrismRA® molecular signature test is unproven and not medically necessary for evaluating likelihood of inadequate response to anti-TNF therapies for rheumatoid arthritis due to insufficient evidence of efficacy.

Definitions

Multi-Gene Panel: Genetic tests that use next-generation sequencing to test multiple genes simultaneously. Also called ~~M~~**m**ulti**-g**~~Multi-G~~ene test, multiple-gene **p**~~P~~anel 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 federal, state or contractual requirements 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
0173U	**Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes**

CPT Code	Description
0175U	Psychiatry (e.g., depression, anxiety), genomic analysis panel, variant analysis of 15 genes
0286U	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism) gene analysis, common variants
0290U	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
*0291U	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score
*0292U	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
*0293U	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
*0345U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
*0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes
*0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes
*0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
*0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes
81479	Unlisted molecular pathology procedure

Codes labeled with an asterisk (*) are not on the Louisiana Medicaid Fee Schedule and therefore may not be covered by the state of Louisiana Medicaid Program.

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** ~~coumadin~~, two to three genes are tested. However, laboratories have developed Multi-Gene Panels **including five or more genes** ~~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 **P**~~p~~**anel**~~Panel~~ testing.

Clinical Evidence

Anxiety and Depression

~~The Pharmacogenomics Knowledgebase~~Knowledge for Personalized Medicine database ~~(PharmGKB) was launched as part of the National Institutes of Health (~~is a NIH)~~ funded Pharmacogenetics Research Network (PGRN) in 2000. Today, this resource focuses on curating peer-reviewed, published literature focused on gene-drug associations. The PharmGKB~~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, 2021).~~).~~

~~The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international organization with membership including clinicians, scientists, laboratorians, and other pharmacogenetic experts with the purpose of facilitating the use of pharmacogenetic test results for patient care. CPIC's goal is to address the barrier caused by difficulty translating genetic laboratory test results into actionable prescribing decisions for applicable drugs by creating freely available, peer-reviewed, evidence-based, and updatable gene/drug clinical practice guidelines. CPIC started as a shared project between (PGRN) and PharmGKB in 2009. CPIC guidelines are indexed in PubMed as clinical guidelines, endorsed by the American Society of Health-System Pharmacists (ASHP) and the American Society for Clinical Pharmacology and Therapeutics (ASCPT), and are referenced in ClinGen and PharmGKB.~~

~~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 and 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)~~

Drug	Gene(s)	Select Associated References
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, HTR2A, and FKBP5 Show Interactive 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)

~~Drug~~	~~Gene(s)~~	~~Select Associated References~~
~~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 **(Tansey et al., 2013),** ~~,~~ which has led to the development of pharmacogenetic **(PGx)** 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.

In a Canadian participant- and rater- blinded randomized controlled trial (RCT), Tiwari et al. (2022) evaluated clinical outcomes for patients with a diagnosis of depression whose treatment was guided by combinatorial pharmacogenomic testing (GeneSight ® Psychotropic or Enhanced GeneSight ® Psychotropic) as compared to treatment-as-usual (TAU). The GAPP-MDD RCT was a 3-arm, 52-week, multi-center trial primarily evaluating symptom improvement using the 17-item Hamilton Depression Rating Scale (HAM-D17) at week 8, as well as secondary outcomes including response (≥50% decrease in HAM-D17) and remission (HAM-D17≤7) at week eight. The participants were randomized 1:1:1 to one of three treatment arms, including two intervention arms and a TAU arm. For the first intervention arm (n=147), the providers received the standard combinatorial pharmacogenomic test report to guide treatment (GEN arm). The second intervention arm included participants (n=152) for whom the providers received an enhanced test report to guide treatment (EGEN – 6 additional genes) and the final arm was TAU (n=138). The researchers found that individuals in the pharmacogenomically guided groups had greater symptom improvement (27.6% versus 22.7%), response (30.3% versus 22.7%) and remission

rates (15.7% versus 8.3%) compared to TAU, but the differences found were not statistically significant. Since they felt that this trial was underpowered to detect statistically meaningful differences in outcomes, the authors did a parallel assessment with the U.S. "GUIDED" trial results (discussed in Greden et al., 2019, below). They found consistent results related to relative improvements in response and remission rates between GAPP-MDD (33.0% response, 89% remission) and GUIDED (31.0% response, 51.0% remission) and concluded that in the context of the Canadian universal healthcare setting, GAPP-MDD and GUIDED RCTs support the use of combinatorial pharmacogenomic testing as an effective tool to help guide treatment of depression.

A systematic review to summarize and assess the state of evidence regarding the use of ~~pharmacogenetic (PGX~~PGx~~)~~ testing in individuals with depression was performed by Aboelbaha et al. in 2021. The researchers queried scientific databases from inception through June 30, 2020 for ~~randomized controlled trials (~~RCTs~~)~~ and systematic reviews which assessed clinical utility of ~~PGX~~ PGx testing for treatment of depression. A total of six systematic reviews and three RCTs ultimately met criteria for inclusion in this study. The results provided evidence on efficacy of ~~PGX~~ PGx testing, with newer RCTs of better quality showing clinical promise regarding efficacy outcomes, especially in participants with gene-drug interactions. The researchers state that ~~PGX~~ PGx testing before initiation of treatment or during therapy may improve efficacy outcome and recommend further studies to assess impact of ~~PGX~~ PGx testing on safety outcomes. Authors Brown et al. (2020), Bousman et al. (2019) and Rosenblat et al. (2018), previously discussed in this policy, were included in the Aboelbaha systematic review.

~~A prospective, two arm evaluation of the clinical utility of Genesight® Psychotropic in guiding treatment decisions for major depressive disorder (MDD) was conducted. The meta-analysis performed by Brown et al. (2020) calculated the overall mean effect of symptom improvement and relative risk ratio (RR) of response and remission referencing four studies and 1,556 patients. When care was guided by combinatorial pharmacogenetics results, significant patient outcomes were reported as compared with MDD patients who received unguided treatment (symptom improvement Δ=10.08%, 95% CI: 1.67-18.50; p=0.019; response RR=1.40, 95% CI: 1.17-1.67; p<0.001; remission RR=1.49, 95% CI: 1.17-1.89; p=0.001). The authors summarized that for MDD patients who have had at least one medication failure, Genesight® Psychotropic guided treatment demonstrated significant clinical utility.~~

~~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~~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~~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~~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~~PGx~~ and TAU groups. The pooled risk ratio for overall treatment response was 1.36 in favor of PGX~~PGx~~ guided treatment compared to~~

~~TAU, and 1.74 for PGXPGx for remission when compare to TAU. The studies were heterogeneous across population, criteria, and PGXPGx testing used.~~

Menchón ~~nchonMenchon~~ et al. (2019) examined the influence of patient characteristics such as age, baseline severity, and duration of episode on the clinical utility of ~~PGX~~ **PGx** testing for psychiatric drugs from the AB-GEN study, a randomized 12-week long study comparing TAU to ~~PGX~~ **PGx** 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~~ **PGx** group (**Pérez** ~~Perez,~~ et al., 2017). However, the ~~PGX~~ **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~~ **PGx** group by 6 weeks, ~~and this~~ **which** was maintained at week 12. The primary dependent variable identified was the number of previously failed medication trials. In the **Me~~n~~nchón**~~chon~~Menchon et al. (2019) reanalysis by patient demographics, additional important variables were identified. Age was important as ~~PGX~~ **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 **in** 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~~ **PGx** arm than TAU. To determine which type of patient is most likely to benefit from ~~pharmacogenetic~~ **PGx** 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~~ **PGx** 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.

Perlis et al. (2018) 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 PGx 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.

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 ($p \leq 0.00001$). 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 (**Pérez** ~~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.~~

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Cardiovascular Disease

The evidence regarding use of multigene PGx testing for cardiac disease is limited at this time. High-quality studies demonstrating improved outcomes related to use of PGx testing in individuals with cardiac conditions and/or undergoing cardiac interventions are required.

Ratner et al. (2022) explored the impact of multigene PGx testing on individuals undergoing percutaneous coronary intervention (PCI) and bone marrow transplant. Frequency of prescription for 65 medications with actionable PGx recommendations were obtained for all participants and a simulation was used to then project the number of opportunities for PGx-guided prescribing. In the PCI group (215 individuals), 66.5% of participants were prescribed at least one medication that had actionable PGx prescribing recommendations available. Using the simulations, if multigene PGx were available, 26.5 prescribing opportunities per 100 individuals undergoing PCI were projected. The authors indicated their belief that multigene PGx testing may offer potential to improve medication prescribing in individuals undergoing PCI. However, additional high quality studies are needed to further investigate the role of PGx testing for individuals undergoing PCI.

**Two hundred and eleven patients from the University of Florida (UF) who underwent percutaneous coronary intervention (PCI) were included in a study to analyze the benefits of genotype-guided prescribing of ~~pharmacogenetic~~ PGx drugs and examine the clinical utility of multigene panel testing. Genotype data for five genes (*CYP2C19, CYP2D6, CYP2C9, VKORC1, SLCO1B1*) was compiled from this cohort. Seventy-seven percent of UF patients exhibited at least one actionable phenotype for these five genes; 32% had opportunities for genotype-guided prescribing of medications. The data was then used as parameter estimates in a simulation model to predict genotype-guided opportunities among privately insured beneficiaries in the MarketScan database who had undergone PCI with at least one and five years of follow-up data (N=105,547 and N=12,462, respectively). Fifty percent of the individuals who had undergone PCI with over ~~1~~one year and 68% with over five years of follow-up were taking at least one ~~Clinical Pharmacogenetic Implementation Consortium (~~CPIC~~)~~ A/B drug in addition to prescribed antiplatelet therapy. A 39% and 52% incidence of genotype-guided prescribing opportunity at one and five years, respectively, was projected. The authors hypothesized that panel-based testing at the time of PCI could result in genotype-driven prescribing decisions in 1/3 of patients, thereby improving therapy outcomes beyond that of *CYP2C19* alone for antiplatelet therapy. (Rouby et al., 2020)~~.

The real-~~-~~world clinical utility of ~~pharmacogenetic~~ **PGx** 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~~ **PGx** 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~~ **PGx** testing did not appear to improve outcomes based on claims analysis.

Anthracyclines

The routine use of PGx panel testing in assessment of risk related to chemotherapy-induced cardiotoxicity (CIC) is not supported by the evidence at this time. Although the initial research shows promise for potential benefit, additional prospective studies with long-term follow-up are needed for validation of the role of PGx related to CIC.

Yang et~~.~~ al. (2021) conducted a systematic review and meta-analysis to examine the correlation between genomic variants and ~~chemotherapy-induced cardiotoxicity (~~CIC~~)~~. The review and analysis included forty-one studies examining the relationship between genetic variants and CIC, including 88 unique genes and 154 single nucleotide polymorphisms (SNPs). The results revealed that six variants had an association with increased risk of CIC, including *CYBA* rs4673, *RAC2* rs13058338, *CYP3A5* rs776746, *ABCC1* rs45511401, *ABCC2* rs8187710, and *HER2*-Ile655Val rs1136201. The authors concluded that this study revealed promising potential benefits of pharmacogenomic testing prior to chemotherapy to minimize the risk of CIC, however further studies are required to validate the prognostic and diagnostic roles of the six identified variants in predicting CIC.

~~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. **Sági** ~~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~~ **PGx** 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, 20192020).~~

Pain Management

Although the evidence for use of PGx panel testing related to pain management is evolving, the use of multi-gene panel testing for predicting response, side effects, dependence or improving overall treatment outcomes is currently not supported as safe or efficacious by the peer-reviewed, published literature.

In a systematic 2022 review, Zobdeh et al. examined the impact of PGx on safety and efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants when they are used for treatment of pain. A total of 25 articles met inclusion criteria and were reviewed in the analysis. Interactions applicable for use in pain management were detected for 10 drug/gene combinations including ibuprofen/*CYP2C9*, celecoxib/*CYP2C*, piroxicam/*CYP2C8*, *CYP2C9*, diclofenac/*CYP2C9*, *UGT2B7*, *CYP2C8*, *ABCC2*, meloxicam/*CYP2C9*, aspirin/*CYP2C9*, *SLCO1B1*, and *CHST2*, amitriptyline/*CYP2D6* and *CYP2C19*, imipramine/*CYP2C19*, nortriptyline/*CYP2C19*, *CYP2D6*, *ABCB1*, and escitalopram/*HTR2C*, *CYP2C19*, and *CYP1A2*. The authors note that the PGx studies identified focused on the role of genes in the *CYP* family for NSAIDs, but the number of studies that investigated the impact of these variants on pain relief are very limited and detected only small impact of *CYP2C8* and *CYP2C9* on therapeutic effect. Overall, there is a lack of well powered studies investigating PGx in individuals being treated for pain with NSAIDs and antidepressants. Although a higher risk for more severe side effects for *CYP2C9* poor metabolizers and NSAIDs was observed, the researchers concluded that larger in vivo studies are required to further investigate the efficacy regarding use of PGx of NSAIDs and antidepressants in pain management.

To determine whether PGx testing may be used to effectively customize postoperative pain management after a total joint replacement, Hamilton et al. (2022) conducted a prospective RCT including 107 individuals undergoing hip or knee arthroplasty. PGx testing was performed using a panel of 16 genes including *CYP2D6*, *CYP2C9*, *OPRM1*, and *CYP1A2*, which have an impact on pharmacodynamics of NSAIDs and many opioids. Participants were blinded and randomized to either a control group (n=46) or custom group (n=61). The control group received prescriptions for oxycodone, tramadol and celecoxib for their postoperative pain. In the custom group, if variants indicating these drugs would not be normally metabolized were found via PGx testing, alternative drugs (hydromorphone, meloxicam) were prescribed. Participants recorded pain levels and medications used for 10 days following surgery and medication used was converted to milligram morphine equivalents (MME). The researchers found that genetic variations to medications in the standard pain management protocol occurred in 22.4% of participants. The 10-day MME in the control group for those individuals who had genetic variants was 162.6 mg. In the custom group, individuals with variants and custom medications used only 86.7 mg in the same timeframe. The control group also had a higher 10-day average pain level than the custom group (4.2 vs. 3.1, respectively, P< 0.05). The authors concluded that with custom postoperative pain medication prescriptions based on results of PGx testing, individuals undergoing hip or knee arthroplasty had better pain control and reduced consumption of pain medication, however they acknowledge that this study was small, especially since the genetic variations of greatest interest are rare.

In a 2021 systematic review, Rodriguez et al. examined the efficacy and safety of opioid therapy guided by PGx testing. Out of 3,794 records found, five met inclusion criteria for data extraction. Of the five studies, two reported significant pain improvement related to PGx-guided therapy in individuals with a high risk CYP2D6 phenotype. The authors concluded that evidence on the safety and efficacy of using PGx testing to guide intervention in opioid therapy for chronic and postoperative pain is very limited.

In 2020 (updated 2022), Hayes published a Clinical Utility Evaluation of pharmacogenetic and pharmacogenomic testing ~~in relation~~related to opioid use disorders. Hayes found insufficient evidence to either predict risk of opioid dependence or improve treatment for patients with opioid use disorder. In addition, a ~~2019~~ Hayes Clinical Utility Evaluation (2019a, updated 2021) found limited, low-quality evidence regarding pharmacogenetic and pharmacogenomic testing prior to prescribing codeine, tramadol, and general opioids with respect to improved opioid related treatment outcomes in adult patients with pain. Lastly, another ~~2019~~ Hayes Clinical Utility Evaluation (2019b updated 2021) found insufficient evidence to report or refute the clinical utility of OPRM1 or COMT genotyping for pain management in patients with organic causes of pain.

Muriel et al. (2019) conducted a six-~~-~~month, observational, prospective study on the use of ~~pharmacogenetic~~ **PGx** 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 **were** 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.

Rheumatoid Arthritis

The body of evidence supporting the PrismRA® test is limited. ~~to one validation study with significant weaknesses, including potential for conflicts of interest and risk of biases, and one health economics modeling study based on this single validation study. These limitations impact the confidence in the quality of the body of evidence. Furthermore, the nature and the uncertainly in the findings of this single study impact negatively the confidence in the potential clinical utility of the test.~~ **For this test to be considered proven and having clinical utility, additional larger and independent studies with better study designs ~~would be~~ are necessary.**

Anti-tumor necrosis factor (TNF) medications are the first tier of rheumatoid arthritis (RA) treatment therapy in over 90% of biologic naïve patients whose disease is not controlled by conventional disease modifying anti-rheumatic drugs (DMARDs); 70% of these RA patients do not attain significant clinical improvement (Mellors et al. 2020). Scipher

Medicine created PrismRA® as a molecular signature test that evaluates the likelihood that an RA patient may not respond to traditional anti-TNF therapy before treatment is initiated. Twenty-three different assessments are made by PrismRA®; the resulting biomarker panel includes **19 gene expression features,** ~~10 disease-associated transcribed single-nucleotide polymorphisms (SNPs), 8 gene expression transcript levels, 2 laboratory measures (C-reactive protein,~~ anti-cyclic citrullinated protein (anti-CCP) and 3 clinical metrics (sex, body mass index, patient disease assessment) which stratify patients based on the likelihood of inadequate response to anti-TNF therapies. ~~The original discovery set of genes is available here: https://www.liebertpub.com/doi/suppl/10.1089/nsm.2020.0007/suppl_file/Supp_Table1.pdf, however the final gene set is unable to be located and likely proprietary~~. Scipher predicts that a 40% increase in response to the first targeted DMARD could have been achieved for RA patients using PrismRA® and that both responders and non-responders have a greater chance of responding to their first biologic/targeted treatment (Mellors et al. 2020).

A Hayes Molecular Test Assessment (2022b) evaluated the clinical validity, utility and analytic validity of Scipher's PrismRA test, noting that the test has undergone changes in the number of risk categories and cutoff values for classification. This Hayes Assessment addresses the PrismRA test in its most current form and previously published analyses of PrismRA which did not evaluate the most current version of the test (or in which the version of the test could not be identified) were excluded from the Hayes assessment. Overall, a very low quality body of evidence was identified to support use of the PrismRA test. Additional studies evaluating PrismRA in larger and more diverse populations are needed.

Jones et al. (2021, included in the 2022b Hayes report) conducted a nonrandomized retrospective assay to assess the analytical and clinical validity of the PrismRA test in individuals with RA who have not responded to tumor necrosis factor-α inhibitor (TNFi) therapy. A total of 174 individual samples from the NETWORK-004 clinical study were analyzed for clinical validity. Of these, 100 were had not undergone any targeted RA therapy and 74 had been exposed to TNFi. The test results classified samples according to non-response prediction with a positive predictive value of 87.7% (95% CI: 78-94%), sensitivity of 60.2% (95% CI: 50-69%), and specificity of 77.3% (95% CI: 65-87%). Three thresholds were used: signal not detected, high, and very high. Accuracy of the test under study was found to be 95.8% for threshold concordance; high repeatability was detected (92.6%) as well as high reproducibility (100%). The authors concluded that PrismRA is a "robust assay" that detects molecular non-response signatures in individuals with RA accurately and reproducibly. Limitations to this study include lack of randomization, small population, wide confidence intervals and inability to determine potential for selection bias due to lack of information regarding the original NETWORK-004 study.

To assess provider decision making and outcomes related to treatment following use of the PrismRA test to inform selection of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in individuals with RA, a prospective cohort study was undertaken (Strand et al., 2022, included in the 2022b Hayes report). In the decision making cohort, 377 individuals met inclusion criteria and were evaluated according to treatment, treatment modifications and physician questionnaire responses. For the clinical outcomes cohort, 212 individuals completing a 12-week follow up visit and a subset of 85 individuals completing a 24-week follow up visit were included; clinical outcomes were evaluated between the subsets based on test results and b/tsDMARD choice. The researchers report that PrismRA test results

informed therapy selection in 73.5% of study participants, noting that when these test results were not incorporated into the decision-making process, 62% of participating providers reported that the deviation from the recommendation was due to insurance-related issues. The American College of Rheumatology criteria for ≥50% responses (ACR50) at 24 weeks for individuals prescribed medication according to PrismRA test results were 39.6%. Individuals whose test results indicated non-response had significantly improved responses to non-TNFi therapies compared to TNFi therapies (ACR50 34.8% vs 10.3%, p-value = 0.05), indicating that predicted non-responders to TNFi therapies are not nonresponders to other types of RA therapy. The researchers concluded that incorporating PrismRA into patient care could significantly improve RA treatment outcomes, however, the study was nonrandomized and nonblinded and there was no comparison group of impacted individuals that did not undergo testing with the PrismRA test. There was also limited racial diversity (79-84% of population was white) and there were significant differences in characteristics, such as age, between the groups. Lastly, there is potential for bias related to affiliations with the test laboratory. Longer term data is required to evaluate persistence and treatment patterns along with disease burden.

Mellors et al. (2020) reported on the Scipher cross cohort, cross platform study that developed the molecular test to predict decreased/non-response (ACR<50) to anti-TNF therapies in biologic-naïve RA patients using the Human Interactome model; 39 RA-associated SNPs were evaluated. Data taken from two cohorts collected from the CERTAIN trial (n=58/patient discovery cohort and n=143/training cohort) were evaluated to produce a drug biomarker panel; laboratory studies included CBC, C-reactive protein, rheumatoid factor titer and anti-citrullinated protein. A validation cohort (n=175) was matched to the training cohort for response rate, age and gender and all validation patients from the CERTAIN study had a clinical disease activity index >10. Results revealed that the biomarker panel identified non-responders with an 89.8% PPV and 86.8% specificity (OR 6.57%). A limitation of this study is that the researchers did not have a single platform or single cohort to analyze. The authors concluded that development and validation of such algorithms to predict drug non-responsiveness shows promise for advancing RA precision medicine treatment and for other complex autoimmune conditions where patients demonstrate inadequate response to therapeutics.

Bergman et al. (2020) developed a decision-analytic model to examine two treatment strategies to evaluate the clinical and economic outcomes of PrismRA® for the first 12 months following initial biologic treatment. They observed clinical decision-making from 175 patients enrolled in the CERTAIN study who received anti-TNF after failing to demonstrate response to conventional synthetic DMARD and modeled clinical decision-making for the same cohort using PrismRA®. In total, 69.7% of patients failed to reach goal of ACR50 in response to anti-TNF treatment. A PrismRA® score of ≥ 11.8 was used to identify patients with a high or very high likelihood or poor/non-response to an anti-TNF treatment. Sixty-eight subjects were predicted to be poor responders: 61 were correctly predicted; 7 were misclassified as they did reach ACR50. With the first treatment strategy, 70% of subjects did not reach ACR50 within 6 months. Subsequently, these subjects received a second-line treatment- either a second anti-TNF treatment (60%) or an alternate treatment (40%); these subjects demonstrated a 20% ACR50 response within 12 months. Subjects who reached ACR50 in the first 6 months stayed on therapy for the entire 12 months. Forty-four percent of patients in the 175-subject cohort were predicted to have achieved ACR50 within the first 12 months of treatment. With the second strategy using PrismRA®, the 68 subjects who were poor responders were assigned to another treatment therapy; 27 reached ACR50 in the first 6 months and the other 107 subjects were prescribed an anti-TNF treatment. Of 107 responders, 61 did not reach ACR50 and were given another mechanism of action as a second-line therapy; 16/61 then achieved ACR50.

Therefore, 57% of subjects from the 175-patient cohort were predicted to reach ACR50 within the first 12 months of treatment. The researchers listed multiple limitations for this study including the lack of sensitivity analysis and the assumption that health care providers will follow with full adherence the PrismRA® test results. The authors concluded that precision medicine and biomarker-driven treatment are a necessary step toward advancing clinical effectiveness and cost-saving for all medications in addition to RA patient treatment.

Johnson and Weinblatt (2018) introduced the PrismRA® test for Scipher Medicine stating that it predicts non-response to all anti-TNF treatments including Humira, Enbrel and Remicade prior to drug prescription. Scipher Medicine reported that preliminary performance suggests a negative predictive value (NPV) of 92% and a true negative rate (TNR) of 50%. Validation of the predictive accuracy of PrismRA® in a clinical trial is ongoing. Scipher is in communication with rheumatologists and payers to determine optimal clinical endpoints. Once the end points are determined from the trial, PrismRA® will be offered commercially as a CAP-proficient, CLIA-certified lab. PrismRA® will allow more RA patients to achieve good response/remission (ACR50) resulting in improved patient outcome and significant cost savings according to the authors.

~~General~~ Other Pharmacogenetic Multi-Gene Panel Testing

The evidence for use of PGx multi-gene panel testing to guide individualized therapies for indications such as multimorbidity, polypharmacy, attention deficit/hyperactivity disorder (ADHD), psychotic disorders and for general use with medication prescription is insufficient at this time.

In a 2022 systematic review, O'Shea et al. sought to establish the efficacy of multi-gene, multi-disease and multi-drug PGx interventions in adults with multiple morbidities and/or prescription polypharmacy in healthcare settings and to inform enactment of PGx-guided treatments in practice. The review included 12 studies assessing multi-medicine PGx in individuals with multiple morbidities or polypharmacy that reported on relevant core outcomes. Studies varied in design and quality; six non-comparative studies, three observational studies and three RCTs were included. Only a narrative analysis was performed due to high levels of heterogeneity in the evidence reviewed, so the results can provide only a high level representation of the impact of PGx testing in multimorbidity and/or polypharmacy. Ultimately, the authors concluded that due to the lack of methodologically robust, high-quality studies with appropriate long term follow-up, no generalized conclusions regarding benefits for patients or health systems could be made based on this review. They assert that there is promise for individualizing therapies through PGx guidance, but further high-quality studies across differing patient care settings are required to establish efficacy.

For use of PGx testing to assist with medication or dose selection for individuals diagnosed with ADHD, a Hayes Clinical Utility Evaluation (2022a) found insufficient evidence to support clinical utility/improved clinical outcomes. The authors suggest that future studies to evaluate PGx testing assessing effects on ADHD symptoms, medication side effects and other clinical outcomes are needed.

A systematic review and meta-analysis evaluating the current evidence regarding impact of PGx testing on hospital admissions and whether PGx leads to changes in medication was published by David et al. in 2021. Five studies focused on hospitalization and five studies focused on medication change were identified for evaluation. Meta-analysis found that changes in medication occurred significantly more often in the PGx test arm in four

of five studies, and all-cause hospitalization occurred significantly less often in the PGx test arm than in treatment-as-usual (TAU) comparator. The researchers share their belief that these results show proof of concept for use of PGx in prescribing that may lead to patient benefit but point out the evidence gaps that exist related to introduction of PGx into health care systems. They feel their analysis will assist with identifying areas where further research is needed, including investigation of the perspectives of health care providers and patients to assist in design of patient-centric PGx-guided care.

A Hayes Clinical Utility Evaluation (2021a) addressed the use of PGx testing to inform selection or dosing of medication for individuals with selected mental health conditions including anxiety disorder, bipolar disorder, depression, schizophrenia spectrum or other psychotic disorder. Hayes concluded that there was lack of consistency in study results and the role of PGx-guided prescribing to improve outcomes in the select mental health disorders detailed above remains uncertain.

Aranz et al. (2019) analyzed the benefits of ~~pharmacogenetic~~ PGx testing of CYP variants for the purpose of adjusting clinical doses of frequently used antipsychotics. Results for patients using ~~pharmacogenetics~~ PGx information (PI) were compared with patients who were treated as usual. Two hundred and ninety patients from three hospitals in Spain with schizophrenia/schizoaffective/ delusional disorders requiring medication were randomized for PI (PharmG+ arm) or treatment as usual (PharmG-arm). Recruitment began when initial treatment was started or when a change in antipsychotic treatment was deemed necessary. One hundred twenty-three patients were genotyped using the commercial Brainchip ~~pharmacogenetic~~ PGx test; 167 patients were treated as usual by adhering to standard clinical practices. Positive and negative scale for schizophrenia (PANSS) and UKU- side effect rating scores were gathered at the beginning and again at 12 weeks to assess effectiveness of treatment. PANSS/UKU values were rated by clinical psychiatrists who were also blinded to the patient's arm. No statistically significant differences were observed in side effects between the two groups. When patients had their dose adjusted based on PharmG+ data (n=123), there was a larger reduction in side effects than those in the PharmG- group but this was not statistically significant (p>0.05). PharmG+ patients who were carriers of *CYP2D6* UMs (ultra-metabolizer) or PMs (poor metabolizer) variants showed statistically larger improvements in global, psychic and other UKU side effects as compared to PharmG- (p=0.02, p=0.05 and p=0.01, respectively). The authors concluded that ~~pharmacogenetics~~ PGx interventions may enhance safety by decreasing the side effects of antipsychotic treatments, however the study did not find evidence of greater efficacy. The researchers also concluded that the results were not unexpected as treatment success may be influenced by more than genomic profiles and describe the effect of drug metabolism as a key factor.

~~MedicationMedication 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 ~~testing~~ 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~~ **in the** treatment of inflammatory bowel disease. Category C was for drugs without a well-defined protocol. In this situation, the ~~pharmacogenetics~~ **PGx** unit would evaluate the therapeutic issue and determine if a ~~pharmacogenetic~~ **PGx** 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~~with ~~well defined~~well-defined protocols and 711 for drugs with ~~pharmacogenetic~~ **PGx** treatment recommendations for certain diseases~~,~~ or ~~had~~ **with** 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~~ **program's total cost** was estimated at 216 € ($254) per patient, and 91% of physicians surveyed said they would now use ~~pharmacogenetics~~ **PGx** 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~~ **PGx** 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, hydrochlorothiazide, lisinopril, and amlodipine. 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~~ **PGx** 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~~ **PGx**, 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.

Clinical Practice Guidelines

American College of Rheumatology (ACR)

In a 2021 ACR guideline (Fraenkel et al.) the PrismRA test is not specifically discussed, however the guideline does reference the following as a "key clinical question requiring further research": Do clinical or biologic markers predict a differential response to DMARDs? They note that the answer to this question is an important gap in knowledge related to management of RA.

ACR has identified eleven measures of disease activity for Rheumatoid Arthritis as a minimum standard for regular use in clinical settings: Disease Activity Score (DAS), Routine Assessment of Patient Index Data 3 (RAPID3), Routine Assessment of Patient Index Data 5(RAPID 5), Clinical Disease Activity Index (CDAI), Disease Activity Score with 28 joints (DAS28-ESR/CP), Patient Derived DAS28, Hospital Universitario La Princesa Index (HUPI), Multibiomarker Disease Activity Score (MBDA score, VectraDA), Rheumatoid Arthritis Disease Activity Index (RADAI), Rheumatoid Arthritis Disease Activity Index D (RADAI-5), Simplified Disease Activity Index (SDAI). (England et al., 2019)

Singh et al. (2016) recommended that the primary goal for RA treatment should be low disease activity and/or clinical remission with a goal of ACR50 or 70 achievement. With moderate to high activity despite DMARD monotherapy, combination DMARD or a TNF1 or non-TNF biologic is preferred over DMARD monotherapy. The guideline states that the use of non-TNF biologics has been proven effective in RA treatment.

Clinical Pharmacogenetics Implementation Consortium (CPIC®)

CPIC® is an international organization with membership including clinicians, scientists, laboratorians, and other PGx experts with the purpose of facilitating the use of PGx test results for patient care. CPIC's goal is to address the barrier caused by difficulty translating genetic laboratory test results into actionable prescribing decisions for applicable drugs by creating freely available, peer-reviewed, evidence-based, and updatable gene/drug clinical practice guidelines. CPIC started as a shared project between the Pharmacogenetics Research Network (PGRN) and the Pharmacogenomics Knowledge Base (PharmGKB) in 2009. CPIC guidelines are indexed in PubMed as clinical guidelines, endorsed by the American Society of Health-System Pharmacists (ASHP) and the American

Society for Clinical Pharmacology and Therapeutics (ASCPT), and are referenced in ClinGen and PharmGKB.

In a recent CPIC guideline, Crews et al. (2021) summarized the evidence regarding *CYP2D6*, *OPRM1* and *COMT* and their impact on opioid analgesia as well as adverse events and provided therapeutic recommendations for *CYP2D6* genotype result usage related to prescription of codeine and tramadol. There is substantial evidence that has linked *CYP2D6* to variations in effect and toxicity of codeine and tramadol, but insufficient evidence to support use of this genotyping for prescribing hydrocodone, oxycodone or methadone. *OPRM1* variants have inconsistently been shown to alter dose requirements for postoperative pain in some opioids, but there is insufficient evidence to clearly demonstrate altered analgesic response to these variants. The most highly studied *COMT* variant is rs4680, but there is no evidence to support association of this variant with adverse effects of opioids and there is mixed evidence for association between *COMT* rs4680 genotype and dosing requirements. For all other variants of *COMT*, there is mixed evidence regarding association between *COMT* and analgesia, opioid dosing and adverse events. Overall, there is limited or weak data for use of *CYP2D6* genotyping for hydrocodone, oxycodone and methadone and for *OPRM1* and *COMT1* in clinical use.

European League Against Rheumatism (EULAR)

Smolen et al. (2019) reported on updates from the EULAR international task force which revisited 2016 policies by conducting literature searches regarding the efficacy and safety of disease modifying antirheumatic drugs (DMARDs). Five principles and 12 recommendations were made for use of conventional synthetic DMARDs; glucocorticoids; biological DMARDs; biosimilar DMARDs; and targeted synthetic DMARDs (Janus JAK kinase inhibitors). Guidance on monotherapy/combination therapy, treatment strategies and tapering on sustained remission are included in addition to cost and sequencing of DMARDs. First treatment is traditionally monotherapy with glucocorticoids, but poor response within 3-6 months recommends stratification to risk factors. In the presence of reduced prognostic factors, biological DMARD or JAK inhibitor should be added to the conventional DMARD. With sustained remission, DMARDs may be lowered but not discontinued.

EULAR recommends arthritis activity be assessed at 1-3-month intervals to determine treatment. "Monitoring of disease activity should include tender and swollen joint counts, patient, and physician global assessments, erythrocyte sedimentation rate, and C reactive protein, by applying a composite measure." Composite measures recommended include the Disease Activity Score with 28 joints, Clinical Disease Activity Index, and Simplified Disease Activity Index. Evaluation of new biomarkers and multibiomarkers for the prognosis and treatment of early arthritis is not recommended by the group. (Combe et al. ~~(~~2017)

International Society of Psychiatric Genetics (ISPG)

In 2021, a group of experts assembled by the ISPG published a narrative review of PGx evidence, product labeling and existing prescribing guidelines for psychotropic medications and the main considerations and concerns related to psychiatric use of PGx testing (Bousman et al., 2021). The group determined that current published literature, product labeling and prescribing guidelines support the use of PGx testing for *CYP2D6*, and *CYP2C19* to inform selection of medication and dosing of multiple common anti-depressant and anti-psychotic medications. They feel the evidence also supports additional testing for human leukocyte antigen genes with use of mood stabilizers including carbamazepine, oxcarbazepine and phenytoin. Screening for variants in *POLG*, *OTC*, and *CSP1* is recommended for valproate screening when there is suspicion of a mitochondrial disorder or urea cycle disorder. Noted in this review is the fact that PGx

testing is not regulated at present and there are many available tests that include genes with little or no support for clinical implementation which could lead to inappropriate medication selection and dosing. Large PGx studies are currently underway, with the expectation that results will lead to further evolution of evidence supporting the use of PGx testing and removal of barriers for appropriate testing. Overall, the group is optimistic regarding the current direction of research and innovation in the field of PGx testing and believes this testing will ultimately become an important tool for use in individuals with psychiatric disorders.

ISPG updated their guidelines on genetic testing (ISPG, ~~2020~~ 2019). Their recommendation regarding ~~pharmacogenetic~~ PGx testing is as follows:

~~Pharmacogenetic~~ PGx testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care. HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, is recommended in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other ~~pharmacogenetic~~ PGx tests at this time is still inconclusive, but when ~~pharmacogenetic~~ PGx testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for *CYP2C19* and *CYP2D6* would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial.

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for adult cancer pain include a section on Principles of PGx, indicating that PGx testing may be considered before initiation or during treatment of pain when concerns of toxicity or lack of analgesic response are present or suspected.

~~**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)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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 **August 18, 2022** ~~September 15, 2021~~)

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Policy History/Revision Information

Date	Summary of Changes
TBD	Coverage Rationale *State-Specific Criteria* • Added language to indicate: ○ The coverage criteria for genetic counseling contained in this policy represents Louisiana Medicaid Managed Care Organization Manual (LA MCO) coverage policy and is set forth below in accordance with State requirements ○ Genetic counseling before and after all genetic testing is required; counseling must consist of at least all of the following and be documented in the medical record: ▪ Obtaining a structured family genetic history ▪ Genetic risk assessment ▪ Counseling of the enrollee and family about diagnosis, prognosis, and treatment *Additional Non State Criteria* • Replaced references to "pharmacogenetic Multi-Gene Panels" with "pharmacogenetic Multi-Gene Panels *(5 or more genes)*" • Revised coverage criteria for use of pharmacogenetic Multi-Gene Panels (5 or more genes); replaced criterion requiring "the individual has a diagnosis of major depressive disorder or anxiety" with "the individual has a diagnosis of major depressive disorder or *generalized* anxiety *disorder*"

	• Added language to indicate the use of the PrismRA® molecular signature test is unproven and not medically necessary for evaluating likelihood of inadequate response to anti-TNF therapies for rheumatoid arthritis due to insufficient evidence of efficacy **Definitions** • Removed definition of "Panel" **Applicable Codes** • Added CPT codes 0173U and 0175U • Added language to indicate: CPT codes 0291U, 0292U, 0293U, 0345U, 0347U, 0348U, 0349U, 0350U are not on the State of Louisiana Fee Schedule and therefore may not covered by the State of Louisiana Medicaid Program **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS149LA.G

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. 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.

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