Pharmacogenetic Panel Testing

Policy Number: 2026T0587Z
Effective Date: October 1, 2026

➲ Instructions for Use

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Related Commercial/Individual Exchange Policy

- Cardiovascular Disease Risk Tests

Community Plan Policy

- Pharmacogenetic Panel Testing

Medicare Advantage Policy

- Molecular Pathology/Molecular Diagnostics/ Genetic Testing

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

The use of pharmacogenetic Multigene Panels (five or more genes) for the evaluation of drug-metabolizer status is unproven and not medically necessary for any indication due to insufficient evidence of efficacy.

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

Definitions

Multigene Panel: Genetic tests that typically use next-generation sequencing to test multiple genes simultaneously; also called multigene test, multiple-gene panel test, and multiple-gene test. (National Cancer Institute Dictionary of Genetics Terms, 2025)

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 guidelines may apply.

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CPT Code	Description
0173U	Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
0175U	Psychiatry (e.g., depression, anxiety), genomic analysis panel, variant analysis of 15 genes
0345U	Psychiatry (e.g., 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
0392U	Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug
0411U	Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6
0419U	Neuropsychiatry (e.g., depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype
0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes
0438U	Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted gene-drug interactions
0460U	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes
0461U	Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes
0476U	Drug metabolism, psychiatry (e.g., major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes
0477U	Drug metabolism, psychiatry (e.g., major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene-drug interactions and reported phenotypes
0516U	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status
0533U	Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (i.e., ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function
0650U	Drug metabolism (adverse drug reactions and drug response), genotyping of 9 genes (i.e., CYP2D6, CYP2C19, G6PD, SLCO1B1, HLA-B*58:01, NAT2, CYP2C9, VKORC1, ABCG2), reported as metabolizer status and transporter function
0652U	Drug metabolism (adverse drug reactions), DNA analysis of 13 genes by targeted genotyping, using saliva or buccal swab, reported as diplotype and metabolizer status
0697U	Obesity, DNA genotyping, analysis of up to 41 genes, buccal swab or blood specimen, patient biometrics, risk-score algorithm to identify a predisposition to up to 4 phenotypes, reported as likelihood to benefit from therapeutics

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CPT Code	Description
81418	Drug metabolism (e.g., pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
81479	Unlisted molecular pathology procedure

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Description of Services

Pharmacogenetics (also called pharmacogenomics) studies how variation in genes impacts the way an individual may respond to certain medications. Differences in genes can account for the reasons why some individuals benefit from a specific medication, while others may not. These differences can also influence the side effects that some individuals experience with a medication, while other individuals have none. (MedlinePlus, 2025)

A pharmacogenetic test is meant to guide treatment strategies, clinical evaluations, and decisions based on its ability to predict response to treatment in particular clinical contexts. 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 Multigene Panels that include five or more genes to proactively evaluate an individual's possible response to many drugs. This policy is designed to address Multigene Panel testing.

Clinical Evidence

Psychiatric Indications

Up to 42% of variance in therapy response for major depressive disorders (MDDs) may be explained by genetic variation (Tansey et al., 2013), which has led to the development of pharmacogenetic/pharmacogenomic (PGx) tests to inform the use of certain psychiatric medications. Currently, multiple combinatorial PGx tests (panels) are commercially available; however, behavioral health clinical practice guidelines (CPGs) and existing published, peer-reviewed evidence do not provide affirmation of the clinical utility of combinatorial PGx tests or guidance on when to use them in the course of clinical care. Additional high-quality studies that use fully blinded designs, along with a focus on the design of effective, evidence-based tools that assess both the likelihood of adverse drug effects and efficacy, are required.

Albers et al. (2025) conducted a meta-analysis to evaluate the clinical utility of a single weighted multigene PGx test in adult individuals with MDD who had experienced failure of at least one prior treatment. Six prospective studies [four randomized controlled trials (RCTs) and two open label], including 3,532 individuals, were analyzed, with primary outcomes measured at 8 to 10 weeks and one study measuring at 24 weeks. Eligible studies enrolled adults who were aged 18 years or older and diagnosed with MDD, and the primary outcomes were assessed using the 17-item Hamilton Depression Rating Scale (HAM-D17) or its differing study design and primary outcome measure (Patient Health Questionnaire-9) scales, defining response as a 50% or greater decline in depression score and remission defined as a HAM-D17 of ≤ 7. A random-effects model was used to pool relative risks (RRs) for response and remission. Individuals whose care was guided by the weighted multigene PGx test were 30% more likely to achieve response (RR ratio, 1.30; 95% CI, 1.16-1.47; $p < 0.001$) and 41% more likely to achieve remission (RR ratio, 1.41; 95% CI, 1.19-1.66; $p < 0.001$) compared with unguided care, with no heterogeneity detected. The authors concluded that prescribing that was guided by a weighted multigene PGx test significantly improved response and remission rates among adults with MDD who had at least one prior treatment failure; this supports its clinical utility for personalized treatment. There are limitations, including inadequate blinding of individuals and prescribers to treatment assignment, recruitment bias from clinician-referred individuals, and potential bias related to industry funding, all of which may increase the likelihood of favorable findings for the PGx intervention. Another limitation is the inability to evaluate publication bias because the small number of included studies prevented formal analysis. The study also has limitations in generalizability, as the sample remained predominantly White despite some inclusion of non-White individuals. Additional limitations include the persistent difficulty in achieving adequate prescriber blinding across PGx studies and the possibility that residual methodological weaknesses could affect interpretation despite the low heterogeneity of results. Publications by Oslin et al. (2022), Greden et al. (2019), and Tiwari et al. (2022), discussed below, were included in this systematic review.

Del Tredici et al. (2025), in a retrospective study using a large U.S. insurance claims database, evaluated the real-world impact of multigene PGx testing (GeneSight®, Myriad Genetics) on two outcomes in patients with MDD [the proportion of patients who filled prescriptions for medications with significant gene-drug interactions (GDIs) and health care resource utilization]. To accomplish this, deidentified claims data were linked to weighted multigene PGx test results for a group of 20,933 adults with MDD. Of the 20,933, 16,965 filled prescriptions both before and after PGx testing. The proportion of patients who filled prescriptions with significant GDIs (incongruent) had a relative reduction of 39.1% after PGx testing

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(26.1% vs 15.9%). Health care resource utilization was also reduced significantly after PGx ($p < 0.001$), with a 38.6% relative reduction in psychiatric-related hospitalizations, 29% reduction in hospitalizations for any reason, and 34.4% decrease in psychiatric emergency department visits. When patients were actively switched from medications that were considered incongruent (higher risk) to congruent (lower risk), a greater relative reduction in hospitalizations was seen (up to 43.9% for psychiatric and 33.9% for all-cause hospitalizations). While these results suggest that PGx may decrease the provision of prescriptions with significant GDIs and potentially reduce health care resource utilization, the study had significant limitations, including its retrospective design, with a lack of a control group and potential for selection bias. Because the study was based on insurance claims data, clinical nuances and/or confounding variables may not have been captured. Lastly, the study was conducted by the developer of the GeneSight test, introducing possible conflicts of interest. Further high-quality studies that include control/comparison groups and evaluate additional relevant clinical outcomes are required.

Zhang et al. (2025) published a systematic review and meta-analysis that compared the effectiveness of PGx-guided antidepressant treatment vs treatment as usual (TAU) in individuals with MDD. Using data from 13 RCTs that were conducted between 2013 and 2024, the authors evaluated response and remission rates at 8 and 12 weeks, while also conducting subgroup and cumulative meta-analyses to assess the influence of ethnicity, disease severity, and gene panel size. The findings revealed that PGx-guided treatment appeared to significantly improve response rates at both 8 weeks (RR, 1.23; 95% CI, 1.05-1.43) and 12 weeks (RR, 1.29; 95% CI, 1.17-1.43) and remission rates at 8 weeks (RR, 1.37; 95% CI, 1.19-1.57). However, remission at 12 weeks did not reach statistical significance (RR, 1.56; 95% CI, 0.93-2.61). Subgroup analyses suggested stronger benefits in Asian populations and in those with difficult-to-treat MDD, but the researchers indicated that these findings require further validation. Cumulative analyses showed that larger PGx panels yielded diminishing clinical returns, suggesting that targeted panels may be more cost-effective. Despite its strengths, the study has notable limitations. PGx panel composition varied in size and content across the trials, as did trial designs and populations of individuals, which may affect generalizability. Ethnic differences in drug metabolism were noted but not fully explored, and long-term outcomes, adverse events, and cost-effectiveness were not addressed. The authors highlighted the need for optimization of multigene panel design and noted the lack of comparative trials that assess the impact of large genetic panel use compared with that of smaller, targeted panels. Lastly, the researchers recommended performance of additional high-quality trials that include larger sample sizes and are focused on outcomes such as adverse effects, long-term remission, and efficacy across more clearly identified levels of disease severity. They further suggested that refining gene panel selection and limiting the use of PGx to difficult-to-treat cases may increase clinical utility. Publications by Vos et al. (2023), Perlis et al. (2020), and Pérez et al. (2017), previously discussed in this policy, and Xu et al. (2024), Oslin et al. (2022), Tiwari et al. (2022), Greden et al. (2019), and Bradley et al. (2018), discussed below, were included in this systematic review.

A Hayes (2025a) Clinical Utility Evaluation assessed the use of PGx testing in individuals with MDD and found uncertain clinical value of PGx when used to guide medication selection/dosage, with the goal of superior clinical outcomes for affected individuals. In total, six publications were included in the evidence review. Although low-quality evidence from some studies demonstrated that PGx may be related to improved short-term outcomes, Hayes determined that significant uncertainty regarding the benefits of PGx compared with TAU persists due to overall inconsistent results among studies. In addition, adequately powered trials that address medication effectiveness/potential side effects, with longer-term follow up, are lacking.

A Hayes (2025b) Clinical Utility Evaluation appraised the value of PGx testing for improving clinical outcomes when used to guide medication selection and dosing in individuals with schizophrenia and found insufficient evidence to support clinical utility. Overall, four studies met the inclusion criteria for the evaluation and were analyzed in the report. Hayes determined that there is significant uncertainty regarding the clinical utility of PGx in individuals with schizophrenia, citing a low-quality, small body of evidence that demonstrated inconsistent results in terms of the clinical impact of therapy informed by PGx vs TAU.

Xu et al. (2024), in an RCT, evaluated the impact of PGx on treatment outcomes in participants with MDD over a 12-week period. The study objective was to determine whether the selection of antidepressant medications based on PGx test results would lead to better response and remission rates, as well as fewer adverse drug effects than TAU. The trial enrolled 665 adults who were diagnosed with MDD and either initiating or switching antidepressant therapy. The PGx testing group (n = 333) underwent PGx testing (including a range of genes), after which clinicians customized a treatment plan that was specific to PGx test results. The control group (n = 332) received TAU based on clinical experience and knowledge of the treating provider. The primary outcome was the proportion of cases with remission/response assessed via the HAM-D; the secondary outcomes included variations in HAM-D scores over time, as well as frequency of reported adverse drug reactions (ADRs). The study results indicate that the PGx-guided group achieved higher response rates at week 8 (39.3% vs 25.7%) and week 12 (48.7% vs 37.3%), higher rates of remission at week 8 (24.0% vs 15.1%) and week 12 (31.0% vs 20.0%), and fewer ADRs overall. The authors concluded that PGx testing allows clinicians to provide

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more personalized medication regimens for individuals with MDD, which ultimately improves treatment outcomes. However, the study has several significant limitations: (1) neither the clinicians providing clinical treatment nor the participants were blinded, which may have introduced bias; (2) the study was conducted at a single center, with a relatively homogeneous sample, limiting the generalizability of the trial's results; and (3) the study included only 12 weeks of follow-up, which is insufficient to fully evaluate the potential treatment benefits of PGx. Additional high-quality RCTs, with longer-term follow-up, are required.

Milosavljević et al. (2024) evaluated the clinical utility of PGx testing in guiding antidepressant therapy in a recent systematic review and meta-analysis. Leveraging data from 15 RCTs and focusing on both dichotomous and continuous outcomes, the researchers measured antidepressant efficacy via assessment of relative and absolute changes in severity of symptoms after 8 weeks of treatment, as well as by response/remission rates; tolerability was estimated by the rate of study discontinuation for any reason. The evaluation revealed that PGx-guided treatment appeared to improve antidepressant efficacy and tolerability compared with TAU, with individuals having higher rates of remission and response after 8 weeks; the PGx group had a 3.4% greater (95% CI, 1.6%-5.2%) reduction in symptom severity than the TAU group. No significant differences in rate of treatment discontinuation for any reason were detected between the PGx and TAU groups at 8 weeks. However, the authors acknowledged several limitations. The heterogeneity among the included trials, such as differences in PGx testing panels, antidepressant regimens, and outcome measures, may affect the generalizability of the findings. Additionally, some trials lacked blinding or had small sample sizes, which could introduce bias. Variability in interpretation and application of PGx results in clinical decision-making also limits the consistency of outcomes. Importantly, the authors pointed out that some currently marketed PGx tools include variants for which relevance to antidepressant treatments is not well established or clearly understood. Despite these challenges, the authors acknowledged the potential of PGx-guided prescribing to personalize depression treatment and improve outcomes in individuals while emphasizing the need for standardized protocols and further large-scale studies. Publications by Oslin et al. (2022), Tiwari et al. (2022), Bradley et al. (2018), and Greden et al. (2019), discussed in detail below, and Vos et al. (2023), Pérez et al. (2017), and Perlis et al. (2020), previously discussed in this policy, were included in this systematic review and meta-analysis.

Tesfamicael et al. (2024), in an umbrella review and meta-analysis, synthesized the existing evidence that addresses the clinical utility and safety of PGx testing when used to guide antidepressant therapy. After a systematic search and screening, six meta-analyses and four systematic reviews, comprising data from a total of greater than 17,000 adults with depression, were included in the umbrella review. Five additional studies, which were all published after 2020, were evaluated via meta-analyses. Pooled effect sizes of RCTs were documented as risk ratios for noncontinuous data and mean differences for continuous data. Overall, the authors observed that PGx-guided prescribing of antidepressants was associated with improved clinical outcomes in individuals with depression after 8 weeks of treatment; those who were receiving PGx-guided therapy were 20% to 49% more likely to respond to antidepressants and 41% to 78% more likely to achieve remission than those receiving TAU. Although these results appear promising, the publication also highlights several important study limitations. The heterogeneity of PGx testing/panels, differences in study designs, and variability in clinical implementation likely contributed to inconsistent findings across trials. Some of the included studies reported no significant benefit with PGx, which underscores the need for standardized testing protocols and clearer clinical guidelines. In addition, several primary studies were included across the various reviews, creating a high proportion of overlap. The majority of studies excluded individuals with comorbid psychiatric conditions, which limits generalizability to broader populations of individuals. Further research is needed to optimize panel design, validate findings across diverse populations, and assess long-term outcomes. Publications by Brown et al. (2022), Oslin et al. (2022), Tiwari et al. (2022), and the Ontario Health Technology Assessment (2021), discussed in detail below, and Perlis et al. (2020), Bousman et al. (2019), and Rosenblat et al. (2018), previously discussed in this policy, were included in this umbrella review and meta-analysis.

Baum et al. (2024) published an update to the 2018 report of the American Psychiatric Association Council of Research Workgroup on Biomarkers and Novel Treatments on the use of PGx tests in treatment selection for individuals with depression. The work group reviewed evidence that was newly published since the prior report (11 clinical trials and five meta-analyses); all studies had primary outcomes that were focused on speed and/or efficacy of response to therapy. Only three trials (using three distinct PGx tests) demonstrated efficacy with statistical significance on the primary outcome measure; two of the studies showing efficacy were small, single-blinded trials, and one was open label. Only one of the trials reviewed addressed adverse effects as a primary outcome. All studies that were examined had significant limitations, such as a lack of full blinding. The work group concluded that recent published data do not support the use of currently marketed multigene panels for guiding selection of therapies for MDD. They recommended further investigation using fully blinded studies and evaluation of promising variants that are not included in currently marketed PGx tests. Studies that are focused on additional purposes of PGx testing, such as evaluation of likelihood of adverse drug effects, are also advised.

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Saadullah Khani et al. (2024) published a systematic review that assessed the influence of PGx testing in individuals who were undergoing antipsychotic treatment. Overall, 13 studies were included in the analysis. The authors determined that while the existing evidence shows either no difference or positive clinical outcomes with PGx-guided prescribing, the studies identified have methodological limitations. Several of the studies were not blinded or randomized, and all studies had fewer than 300 individuals. The reviewers indicated that confounding factors such as selection bias were underestimated as well. With these limitations, the researchers recommended interpreting the results with caution. High-quality studies are needed to evaluate the specific benefits of PGx testing for mental health conditions.

Skokou et al. (2024) reported findings that were specific to psychiatric-related PGx testing from the PREPARE (Pre-Emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions) study. PREPARE was a multicenter, open-label, prospective study of the clinical utility of PGx-guided treatment that used a 12-gene PGx panel and investigated the occurrence of ADRs. In this publication, outcomes that were focused specifically on 1,076 participants with schizophrenia, MDD, or bipolar disorder were described. The primary goal of this investigation was to evaluate the impact of PGx-guided therapy on incidence of ADRs in participants with the above noted psychiatric indications. Although each sample was genotyped for 12 genes, only *CYP2C19* and/or *CYP2D6* were considered as part of this analysis, as these are the two pharmacogenes related to the metabolism of psychiatric medications. The researchers found that participants with an actionable phenotype in the PGx-guided arm of the study (n = 25) had 34.1% fewer ADRs than those in the control arm (n = 36). In addition, 41.2% fewer hospitalizations occurred, and less polypharmacy in the PGx-guided arm was observed (n = 124 prescribed at least four psychiatric drugs in the PGx-guided arm vs n = 143 in the control arm). Nine deaths were reported in the control arm compared with only one death in the PGx-guided arm. The authors determined that PGx-guided therapy may have a helpful impact on individuals with psychiatric diagnoses. However, the proportion of participants with an actionable genotype in this study was small (~25%), which impacted statistical significance. This study focused only on occurrence of ADRs; drug efficacy was not evaluated. As such, an additional study that is focused on drug efficacy, as well as occurrence of ADRs, is recommended. In addition, the study focused only on the impact of *CYP2C19* and *CYP2D6* and did not incorporate findings from other pharmacogenes that may be included in larger PGx panels.

Kang et al. (2023) investigated the effectiveness of multigenetic PGx-guided treatment (MPGT) compared with that of TAU in an RCT that comprised hospitalized Han Chinese men with schizophrenia. Conducted across two hospitals from 2020 to 2022, the study enrolled 210 male participants who were aged 18 to 60 years and had a clinical diagnosis of schizophrenia. Participants were randomized to receive either MPGT or TAU over a 12-week period, with the primary outcome being the percentage change in Positive and Negative Syndrome Scale scores at week 6. The secondary outcomes included response and symptomatic remission rates. The researchers found that participants in the MPGT group experienced significantly greater symptom improvement, with a 74.2% reduction in Positive and Negative Syndrome Scale scores compared with 64.9% in the TAU group (95% CI, 4.4-14.1 percentage points; $p < 0.001$). Additionally, the MPGT group had higher response rates (82.3% vs 64.9%) and remission rates at week 12 (62.8% vs 45.4%). Notably, the PGx-guided group achieved these outcomes with relatively lower medication doses. While the study included both participants with a first episode and relapse, subgroup analyses were exploratory and did not detect statistically significant differences between the groups. No serious adverse events were reported during this trial. The study had several limitations. It focused exclusively on hospitalized male participants of Han Chinese ethnicity, which may limit generalizability to other populations. The trial did not assess the long-term outcomes of PGx-guided treatment; this is an area that warrants future investigation in well-designed trials with larger samples sizes. Additionally, prescribing physicians were not blinded to the study groups, which may have created bias. The authors cautioned that while the findings are promising, further research is needed to design appropriate PGx testing panels for diverse populations and validate MPGT in broader clinical settings and populations.

Bunka et al. (2023) conducted a meta-analysis and rapid review focused on appraising the impact of PGx testing on clinical outcomes compared with that of TAU in individuals with MDD. The analysis incorporated results from 10 RCTs. All PGx decision-support tools that were used for depression included *CYP2C19* and *CYP2D6* pharmacogenes, but no specific test or panel was evaluated by this review; rather, the review focused on PGx testing in general. Based on this analysis, the authors determined that PGx-guided care for MDD more often resulted in remission and response compared with TAU. Despite this finding, notable limitations exist, including a high risk of bias and inconsistencies between the various trials; additional high-quality research is needed. Further studies should incorporate diverse populations and address the lack of evidence, focusing on adverse effects, as well as the measurement of long-term efficacy, including rates of recurrence. Studies by Greden et al. (2019) and Bradley et al. (2018), discussed below, and Pérez et al. (2017), previously discussed in this policy, were included in this analysis.

Wang et al. (2023), in a systematic review and meta-analysis of RCTs, investigated the impact of using PGx testing to guide treatment on clinical outcomes in individuals with MDD. Overall, 11 studies, comprising 5,347 individuals, were included in the evaluation. Various marketed tests, with differing numbers of genes, were used in the studies. The authors

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noted that most of the studies were considered to have a high risk of bias, as the studies were industry funded. The group of individuals whose treatment was guided by PGx testing was associated with an increased response rate at week 8 [odds ratio (OR), 1.32; 95% CI, 1.15-1.53; eight studies; 4,328 individuals] and week 12 (OR, 1.36; 95% CI, 1.15-1.62; four studies; 2,814 individuals) compared with the usual treatment group. In addition, the group with pharmacogenomically guided treatment had an association with increased remission rates at week 8 (OR, 1.58; 95% CI, 1.31-1.92; eight studies; 3,971 individuals) and week 12 (OR, 2.23; 95% CI, 1.23-4.04; five studies; 2,664 individuals). However, no significant differences in either response rate or remission rate were found between the two groups at week 4 or week 24. The meta-analysis also found that medication congruency in 30 days showed a significant reduction in the PGx testing group vs the usual care group (OR, 2.07; 95% CI, 1.69-2.54; three studies; 2,862 individuals). A subgroup analysis revealed a significant difference between the Asian subgroup and the Caucasian subgroup, possibly due to the subgenotype of allele frequencies of gene variants. The authors concluded that overall, the results of this analysis indicate that pharmacogenomically guided treatment led to faster clinical remission or response in individuals with MDD but resulted in no difference in final response or remission at the end of the pharmacogenomically guided treatment. These results differ from those of previous meta-analyses, which showed overall higher response/remission rates in individuals with MDD who underwent pharmacogenomically guided treatment compared with those who underwent usual treatment. The researchers speculate that the lack of significant changes at week 4 may be due to the long onset time of antidepressants and that the lack of significant changes at week 24 may be due to the PGx testing showing an accelerated process of excluding unsuitable antidepressants for individuals with MDD. Ongoing high-quality studies are recommended to continue the assessment of the benefits of PGx testing, especially across differing populations and ethnic groups. Publications by Oslin et al. (2022), Tiwari et al. (2022), Greden et al. (2019), and Bradley et al. (2018), discussed below, and Perlis et al. (2020), previously discussed in this policy, were included this systematic review.

Brown et al. (2022) performed a systematic review and meta-analysis of 13 clinical trials, which comprised 4,767 individuals with MDD. Prescribing recommendations for individuals who were in the PGx-guided treatment group were based on their *CYP2C19* and *CYP2D6* genotypes, while treatment recommendations for those in the TAU group were based on current Australian guidelines for the prescribing of antidepressant medications. The study findings revealed that the application of PGx test results for treatment guidance in individuals with MDD resulted in a modest but significant increase in the remission of depressive symptoms. Across all trials, individuals who were receiving PGx-guided treatment for MDD were 41% (95% CI, 15%-74%) more likely to reach remission than those whose treatment was not guided by PGx. However, the authors highlighted that the trials that were included in this systematic review and meta-analysis used tests that assessed variants in genes beyond *CYP2C19* and *CYP2D6* (e.g., *SLC6A4, HTR2A*) since this additional testing is often included in panels marketed by various commercial laboratories, even though no dosing guidelines for these genes are available. In addition, many of the test panels used in these trials included proprietary algorithms that could result in conflicting recommendations, which highlights the need for standardization and regulation of PGx testing in the context of MDD treatment. Publications by Oslin et al. (2022), Tiwari et al. (2022), Bradley et al. (2018), and Greden et al. (2019), discussed below, and Perlis et al. (2020), previously discussed in this policy, were included in this systematic review and meta-analysis.

Oslin et al. (2022) conducted an RCT, which included 1,944 participants with MDD, to assess the impact of PGx testing for drug-gene interactions on the selection of antidepressant medications and response of depression symptoms compared with that of usual care. Eligible participants had MDD and were starting therapy or switching therapy, including a single antidepressant. Participants with active substance disorders, mania, psychosis, or concurrent treatment with other specified medications were excluded. In the PGx-guided group (n = 966), results from a commercial PGx test (GeneSight, Myriad Genetics) were provided to clinicians who were overseeing the care for that group. The comparison group (n = 978) received usual care (access to PGx results were provided after 24 weeks). The outcomes included the proportion of prescriptions with predicted drug-gene interactions written within 30 days of randomization and remission of the symptoms of depression, as assessed by the Patient Health Questionnaire-9. An assessment of outcomes was performed at weeks 4, 8, 12, 18, and 24 by raters who were blinded to clinical care and study randomization. Of the 1,944 participants randomized, 79% completed the full 24-week evaluation. The estimated risk of receiving an antidepressant with none, moderate, or substantial drug-gene interactions for the group with care that was guided by PGx testing results was 59.3%, 30.0%, and 10.7%, respectively. In the usual care group, the risk was determined to be 25.7%, 54.6%, and 19.7%. Prescriptions with no predicted drug-gene interaction were provided for 45% of participants in the pharmacogenomically guided group compared with 18% of participants in the usual care group; this is a statistically significant difference. Overall, rates of remission over the course of 24 weeks were higher in participants whose care was directed with PGx testing than those who were receiving usual care (OR, 1.28; 95% CI, 1.05-1.57; $p = 0.02$; risk difference, 2.8%; 95% CI, 0.6%-5.1%). However, remission rates were not significantly higher in the pharmacogenomically guided group at 24 weeks. The authors concluded that in participants with MDD, offering PGx testing for drug-gene interactions decreased prescriptions of medications with predicted drug-gene interactions compared with usual care. Use of test results had small positive impacts on symptom remission (especially early in the trial) that did not persist at 24 weeks.

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Tiwariet al. (2022), in a Canadian participant- and rater-blinded RCT, evaluated clinical outcomes in participants with a diagnosis of depression whose treatment was guided by combinatorial PGx testing (GeneSight Psychotropic or Enhanced GeneSight Psychotropic) compared with those in participants who were receiving TAU. The GAPP-MDD (Genomic Applications Partnership Program-Major Depressive Disorder) RCT was a three-arm, 52-week, multicenter trial that primarily evaluated symptom improvement using the HAM-D17 at week 8, as well as secondary outcomes, including response (≥ 50% decrease in HAM-D17) and remission (HAM-D17 ≤ 7) at week 8. 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 PGx 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; six additional genes), and the final arm received TAU (n = 138). The researchers found that participants in the pharmacogenomically guided groups had greater symptom improvement (27.6% vs 22.7%), response (30.3% vs 22.7%), and remission rates (15.7% vs 8.3%) than those receiving 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 performed a parallel assessment with the U.S. GUIDED (Genomics Used to Improve Depression Decisions) trial results (discussed in Greden et al., 2019, below). They found consistent results that were 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 health care setting, the GAPP-MDD and GUIDED RCTs support the use of combinatorial PGx testing as an effective tool to help guide treatment of depression. Noted limitations include the lack of diversity in the cohort, no assessment of adherence to treatment, the lack of assessment of the impact of polypharmacy on outcomes, and the lack of blinding of clinicians who were evaluating participants.

A Hayes (2022a; updated 2025) Clinical Utility Evaluation found insufficient evidence to support clinical utility or improved clinical outcomes for the use of PGx testing to guide medication or dose selection in individuals who were diagnosed with attention-deficit/hyperactivity disorder. The authors suggested that future studies to evaluate PGx testing, assessing the effects on attention-deficit/hyperactivity disorder symptoms, medication side effects, and other clinical outcomes, are needed.

An Ontario Health Technology Assessment (2021), which included a systematic review of the literature, evaluated the safety, effectiveness, and cost-effectiveness of multigene PGx tests designed with decision-support tools to aid in the treatment of individuals with MDD. Fourteen studies, including evaluation of six multigene PGx tests (GeneSight, NeuroIDgenetix®, CNSDose, Neuropharmagen, Genecept, and one unspecified test), were reviewed. The heterogeneity of the available multigene PGx tests, as well as the study design, populations included, and outcomes reported, were noted. The effectiveness of the six tests that were evaluated was inconsistent; the clinical utility of one test may not apply to the others. Little to no differences were found in score changes on the HAM-D17 in individuals who underwent PGx testing compared with those who were treated with usual care; however, some of the tests showed promising results in terms of response to treatment or remission of the individuals' symptoms.

Aboelbaha et al. (2021) conducted a systematic review to summarize and assess the state of evidence regarding the use of PGx testing in individuals with depression. The researchers queried scientific databases from inception through June 30, 2020, for RCTs and systematic reviews that assessed the clinical utility of PGx testing for the treatment of depression. A total of six systematic reviews and three RCTs ultimately met the criteria for inclusion in this study. The results provided evidence of the efficacy of PGx testing, with newer RCTs of better quality showing clinical promise regarding efficacy outcomes, especially in individuals with GDIs. The researchers stated that PGx testing before initiation of treatment or during therapy may improve efficacy outcomes, and they recommended further studies to assess the impact of PGx testing on safety outcomes. Publications by Brown et al. (2020), Bousman et al. (2019), and Rosenblat et al. (2018), previously discussed in this policy, were included in the Aboelbaha et al. systematic review.

A Hayes (2021; updated 2024) Molecular Test Assessment evaluated the GeneSight Psychotropic test, which is a PGx gene panel that is designed to assess gene-drug interactions to aid health care providers in treatment decision-making for individuals with mental health conditions. Hayes found no peer-reviewed studies that addressed analytic or clinical validity but did reference four studies (none of which included the current 15-gene configuration of the test) that reported on the GUIDED trial. Overall, Hayes found insufficient evidence that supports the use of GeneSight for mental health disorders at this time. Since the original 2021 publication, additional studies that address the clinical utility of GeneSight have been published; however, the most recent review of the Hayes assessment indicates that the newly published studies are unlikely to change the current rating of D2.

Greden et al. (2019) conducted the GUIDED study, which was a 24-week RCT (April 2014 to February 2017) that compared active treatment guided by PGx information with active treatment receiving TAU for MDD (included in the Hayes, 2021, GeneSight Psychotropic Molecular Test Assessment). Overall, 60 sites participated; participants were

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referred to the study when they or their clinician reported an inadequate response to at least one antidepressant. The average number of failed medications in the cohort was three, making this a difficult-to-treat population. Genotyping was performed for eight genes: *CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A*, and *SLC6A4.* The results were evaluated and reported using a proprietary PGx algorithm from Assurex Health. Participants were blinded to the study arm but clinicians were not because they needed to consult the PGx results to guide treatment. Using the results to guide treatment was not mandated. Participants were assessed at 4, 8, 12, and 24 weeks using the HAM-D17, which was administered by blinded raters. A total of 1,167 enrolled participants made it through week 8, with 607 in the TAU and 560 in the PGx-guided groups. 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 a ≥ 50% decrease in depression, was greater in the PGx arm (26%) than the TAU arm (20%). The depression remission rate, defined as a score of ≤ 7 on the HAM-D17, was 10% with TAU and 15% with PGx (p = 0.007). Additionally, at week 8, no difference between the groups in reported side effects was observed. When participants 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 rate increased to 91%, and the TAU group was unchanged. After completing 8 weeks, clinicians in the TAU arm were unblinded and could use the PGx results if they chose. A total of 913 participants completed week 24, with 456 in the TAU and 457 in the PGx-guided arms. Overall, in the PGx group, HAM-D17 scores decreased by 42.5% 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, a significant difference in response and remission was observed in the PGx group on other measures.

Bradley et al. (2018) conducted an RCT to evaluate the clinical utility of the NeuroIDgenetix test, which incorporates a panel of 10 genes with selected polymorphisms and a proprietary algorithm, for guiding treatment decisions in individuals with depression and anxiety. Genes in the test included *CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, COMT, HTR2A*, and *MTHFR*. Participants were identified from 20 independent clinical sites in the U.S. that represented psychiatry, internal medicine, family medicine, and obstetrics and gynecology. Overall, 685 participants were included in the study, ranging in age from 19 to 87 years, and all had a diagnosis of depression or anxiety using the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) criteria and verified by the Mini International Neuropsychiatric 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 participants but was only shared with the physicians of those in the PGx arm. Participants 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 that was developed by external psychiatric consultants, and a blinded clinician ranked the adverse events on a severity scale. The PGx testing group had a greater response and remission rate (ORs of 4.72 and 3.54, respectively) than the TAU group at 12 weeks. In the anxiety group, those who received testing had a higher response rate at 8 and 12 weeks, with an OR of 1.76, compared with the TAU group. At the 2-week follow-up, physicians made at least one medication change in 81% of those receiving testing compared with 64% in the control group. No difference was found in adverse drug events between the two treatment groups. In a post hoc analysis in the inadequately controlled cohort, improvements in remission (42% vs 27%; p = 0.03) and response rates (62% vs 44%; p = 0.01) 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. Overall, 98 European-American participants participated in a venlafaxine XR clinical trial for GAD, with 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 weeks 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 a 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 the antidepressant venlafaxine XR on GAD.

Cardiovascular Disease

The evidence regarding the use of multigene PGx testing for cardiac disease is limited. High-quality studies that demonstrate improved outcomes related to the use of PGx testing in individuals with cardiac conditions and/or those who are undergoing cardiac interventions are required.

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Ratner et al. (2022) explored the impact of multigene PGx testing on individuals who were undergoing percutaneous coronary intervention (PCI) and bone marrow transplant. The frequency of prescription for 65 medications with actionable PGx recommendations were obtained for all individuals, 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 individuals were prescribed at least one medication that had actionable PGx prescribing recommendations available. Using the simulations, if multigene PGx was 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 who are undergoing PCI. However, additional high-quality studies are needed to further investigate the role of PGx testing in individuals who are undergoing PCI.

Rouby et al. (2020) enrolled 211 participants from the University of Florida who underwent PCI in a study to analyze the benefits of genotype-guided prescribing of PGx drugs and examine the clinical utility of multigene panel testing. Genotype data for five genes (*CYP2C19, CYP2D6, CYP2C9, VKORC1,* and *SLCO1B1*) were compiled from this cohort. Overall, 77% of participants had at least one actionable phenotype for these five genes; 32% had opportunities for genotype-guided prescribing of medications. The data were 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 1 and 5 years of follow-up data (n = 105,547 and n = 12,462, respectively). In total, 50% of the participants who had undergone PCI with over 1 year of follow-up and 68% with over 5 years of follow-up were taking at least one Clinical Pharmacogenetics Implementation Consortium (CPIC®) A/B drug in addition to prescribed antiplatelet therapy. A 39% and 52% incidence of genotype-guided prescribing opportunity at 1 and 5 years, respectively, was projected. The authors hypothesized that panel-based testing at the time of PCI could result in genotype-driven prescribing decisions in one-third of individuals, thereby improving therapy outcomes beyond that with *CYP2C19* alone for antiplatelet therapy.

Billings et al. (2018) studied the real-world clinical utility of PGx testing for managing cardiovascular disease. A retrospective cohort of patients 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. Patients who received PGx testing that included *CYP2C19, CYP2C9, VKORC1, F5, F2*, and *MTHFR* were matched to controls based on demographics and diagnoses. PGx testing was ordered at the physician's discretion and was not influenced by the study. The total number of patients tested was 11,060, and 178,096 matched controls were identified. The outcomes evaluated through claims data included pharmacy costs, medical costs, emergency department visits, outpatient visits, and emergency department stays, controlling for demographics, coverage type, low income, cardiovascular disease, and other comorbidities, 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 PGx testing did not appear to improve outcomes based on claims analysis.

Anthracyclines

The routine use of PGx panel testing in the 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.

Hansson et al. (2025) conducted a systematic review that followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to summarize evidence on PGx associations with chemotherapy-induced toxicities in pediatric oncology patients with solid tumors. Overall, 59 studies met the inclusion criteria, including 15 cohort and nine case-control designs, mostly retrospective, enrolling children who were aged 18 years or younger. Risk of bias was assessed using the ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) tool, and 24 articles with low to moderate risk were summarized. The primary outcomes were chemotherapy-induced toxicities, including myelosuppression, hepatotoxicity, ototoxicity, and cardiotoxicity, which were defined using standardized criteria such as CTCAE (Common Terminology Criteria for Adverse Events), World Health Organization, AHA, and audiometric classifications. Significant associations were identified between methotrexate-related myelosuppression and *ABCC2, CYP2B6, CYP4F8,* and *ERCC2*, such as methylenetetrahydrofolate reductase (*MTHFR*), *SLCO1B1*, and *SXR*, and between hepatotoxicity and *ABCB1, ABCC2*, and gamma-glutamyl hydrolase (*GGH*), such as methylenetetrahydrofolate reductase (*MTHFR*) and *SXR.* For platinum-based drugs, ototoxicity was associated with *ABCC3*, catechol-O-methyltransferase (*COMT*), *ERCC2*, glutathione S-transferase pi (*GSTP1*), glutathione S-transferase theta *(GSTT1*), megalin gene (*LRP2*), and *SLC22A2* and on the activity of the enzymes thiopurine S-methyltransferase (*TPMT*); anthracycline-induced cardiotoxicity (ACT) was linked to *CBR2, CELF4, GSTM1, HAS3*, retinoic acid receptor gamma (*RARG*), and *SLC28A3*, with dose-dependent effects for *HAS3* and *CELF4*. The authors concluded that PGx associations with chemotherapy-induced toxicities in pediatric oncology are complex and variable, with no single SNPs showing a strong, consistent relationship across studies. Key limitations include the marked heterogeneity in sample size, individuals' age, disease type, cumulative dosage, definitions of toxicity, and use of protective or concurrent toxic

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treatments. There are additional limitations related to confounding, as several studies did not fully identify or control potential confounders despite some efforts to minimize them. Chemotherapeutic regimens frequently combined multiple agents, making it difficult to attribute observed toxicities to a single drug or to possible synergistic effects. Other concomitant medications, such as aminoglycosides and furosemide, may have contributed directly to toxicities or indirectly altered drug metabolism, potentially obscuring true associations.

Wong et al. (2025), in a systematic review and meta-analysis, investigated whether PGx testing can effectively predict and prevent ACT in children who were undergoing cancer treatment. Anthracyclines are cornerstone chemotherapy agents that are used in nearly 60% of pediatric cancers. However, they carry a significant risk of cardiotoxicity, with up to 16% of treated children developing heart failure. The authors reviewed 37 studies that involved 26,446 pediatric individuals, focusing on genetic variants associated with ACT and the predictive accuracy of PGx testing. They identified five cardiotoxic variants (*ABCC2* rs8187710, *ETFB* rs79338777, *GPR35* rs12468485, *HNMT* rs17583889, and *UGT1A6* rs17863783) and two cardioprotective variants (*GSTA2* rs2180314 and *HFE* rs1799945) that were significantly associated with ACT. An additional variant (*ABCC5* rs7627754) that significantly improved cardiac function metrics (left ventricular ejection fraction and fractional shortening) was identified as well. PGx models that combined genetic and clinical data showed higher predictive accuracy (area under the curve, 0.67-0.87) than models using clinical data alone (area under the curve, 0.57-0.81). Despite relatively promising findings, the authors cautioned that the certainty of evidence is very low due to imprecision in summary effect estimates; inconsistency across studies; potential publication bias, with a tendency to report positive findings; ethnic homogeneity in study populations, limiting generalizability; and a lack of standardized testing panels. In addition, commercially available PGx tests do not necessarily cover all relevant variants. The authors concluded that while PGx testing shows potential for identifying children who are at risk of ACT and improving clinical outcomes, robust, ethnically diverse studies are needed before widespread clinical adoption can be recommended. The publication by Sági et al. (2018), discussed below, was included in this systematic review and meta-analysis.

Stafford et al. (2024) conducted a study that assessed 253 adolescent and young adult (AYA) cancer survivors who had previously undergone anthracycline treatment to determine whether previously identified genetic variants associated with anthracycline-induced cardiac dysfunction in children similarly impacted this population; 45 gene variants were evaluated. In these 253 AYAs, four variants associated with cardiac dysfunction were detected: *SLC10A2*:rs7319981 ($p = 0.017$), *SLC22A17*:rs4982753 ($p = 0.019$), *HAS3*:rs2232228 ($p = 0.023$), and *RARG*:rs2229774 ($p = 0.050$). Interestingly, *HAS3*:rs2232228 and *SLC10A2*:rs7319981 impacted the AYA cancer survivor group in reverse of the manner that has been reported for childhood cancer survivors. Further evaluation of host genes was performed to assess for additional genetic variants associated with cardiotoxicity in AYA cancer survivors. The host genes were also analyzed in a panel of induced pluripotent stem cell–derived cardiomyocytes to determine changes in levels of expression when doxorubicin was used for treatment. The reviewers observed significant upregulation of *HAS3* and *SLC22A17* expression ($p < 0.05$) and nonsignificant anthracycline responsivity for *RARG*. Overall, they concluded that there appears to be a genetic influence on cardiac dysfunction in AYAs with cancer, but this study suggests that the role of genetics may vary between children and AYAs who survive cancer. Further study is required to better understand the role of PGx in determining the risk of anthracycline-induced cardiac dysfunction and the differences in associated variants based on age and other factors.

Yang et al. (2021) conducted a systematic review and meta-analysis to examine the correlation between genomic variants and CIC. The review and analysis included 41 studies that examined the relationship between genetic variants and CIC, including 88 unique genes and 154 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 felt that this study revealed promising potential benefits of PGx 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. The publication by Sági et al. (2018), discussed below, was included in this systematic review and meta-analysis.

Sági et al. (2018) conducted genotyping of 26 genes and 70 SNPs associated with anthracycline metabolism and a retrospective review of medical records of 622 children with acute lymphoblastic leukemia (ALL) and 39 children with osteosarcoma; the patients were treated between 1989 and 2015 in Hungarian pediatric oncology centers. Anthracyclines are an important category of chemotherapeutic agents for hematologic and solid tumors but are associated with a high rate of ACT that can result in symptoms during therapy or even years after therapy is completed. Those with comorbidities such as Down syndrome or prior cardiac findings were excluded. Blood samples were taken from children with ALL in remission. All patients were followed up with echocardiography routinely during and after treatment, and a retrospective chart review examined the following time points: at baseline (used as a control), in the acute phase, during oral maintenance, at the end of treatment, 2 to 3 years post diagnosis, 5 to 10 years post diagnosis, and 10 to 15 years post diagnosis. SNPs in *ABCC2*, *NQO1*, *SLC22A6*, and *SLC28A3* were associated with decreased fractional shortening and ejection fraction, particularly in the 5- to 10-year period after diagnosis. *NQO1* SNP rs1043470 T was associated with lower left ventricular function in the acute phase and 5 to 10 years post diagnosis. *CYP3A5* rs4646450 TT was found in

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17% of patients with ALL who had ACT with a fractional shortening of less than 28 and appeared to be more prominent in ACT overall, particularly in boys and the ALL group. Additional prospective studies, with long-term follow-up, are needed to further understand how PGx testing can contribute to understanding ACT.

Pain Management

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

Annis et al. (2025) investigated the relationship of genetics and persistent opioid use following surgery, with a focus on identifying specific genetic variants that may contribute to opioid use disorder (OUD). The researchers analyzed data from approximately 40,000 individuals in the Michigan Genomics Initiative. The cohort included 3,198 cases of persistent opioid use and 36,321 surgically exposed controls, all of non-Hispanic European ancestry. The study aimed to evaluate the reproducibility of previously reported genetic associations with OUD by examining 72 prior genetic studies. Among 80 unique genetic signals, only 12 showed nominal associations ($p < 0.05$); six of these were in the *OPRM1* gene that encodes the μ-opioid receptor, which is a key target of opioid drugs. The most significant variant identified in *OPRM1* was rs79704991-T (OR, 1.17; $p = 8.7 \times 10^{-5}$). Two *OPRM1* variants survived multiple testing correction, which indicates a significant association. The authors asserted that these findings suggest a shared biological basis between persistent opioid use and OUD, highlighting *OPRM1* as a potentially important genetic driver. Interestingly, two genes that are commonly associated with OUD, *OPRD1* and *DRD2/ANKK1*, had no signals in the Michigan Genomics Initiative. The study has several notable limitations. The cohorts were limited to individuals of non-Hispanic European ancestry, which may reduce generalizability to other ethnic groups. Prescription data were used to define persistent opioid use; this may not fully capture all aspects of OUD. The study did not take other nongenetic influences into account (e.g., socioeconomic status, mental health, pain severity), which could impact outcomes. Additionally, despite analyses of many previously reported loci, few of these showed reproducible associations, which raises questions regarding the accuracy of previous studies and demonstrates the need for continued research in the field of opioid genetics.

Jethwa et al. (2025) conducted a systematic review and meta-analysis to evaluate whether PGx-guided opioid prescribing improves pain management outcomes compared with standard prescribing practices. Following PRISMA guidelines, the researchers identified six RCTs (from a total of 2,496 screened publications) that met the inclusion criteria for this review and analysis. The assessment revealed that PGx-guided prescribing was associated with a statistically significant reduction in opioid use (standardized mean difference, -0.38; 95% CI, -0.67 to -0.08; $p = 0.01$), but no significant difference was found in pain intensity between the PGx and standard prescribing groups (standardized mean difference, 0.31; 95% CI, -0.89 to 0.27; $p = 0.30$). Only one trial reported adverse events, showing a statistically significant reduction in the PGx group. This review and analysis was limited by the relatively small number of included RCTs, which inhibited the generalizability and overall statistical power of the reported findings. In addition, the studies varied in terms of the populations of individuals, types of opioids used, and genes/genetic markers evaluated. Reported data on adverse events were minimal (limited to a single study), which inhibits the ability to draw reliable conclusions regarding safety. Lastly, most of the studies had short follow-up periods, which may not capture longer-term outcomes or delayed adverse effects. The authors concluded that PGx-guided opioid therapy shows promise in reducing opioid consumption and potentially lowering adverse events but does not yet demonstrate clear benefits. The authors emphasized the need for larger, more rigorous trials and standardized protocols to better understand the clinical utility of this personalized approach. Publications by Kraus et al. (2024), Agulló et al. (2023), and Hamilton et al. (2022), discussed below, were included in this systematic review and meta-analysis.

Escorial et al. (2024) conducted an observational study in 806 individuals with chronic noncancer pain (CNCP) who were receiving long-term opioid therapy to help develop a predictive model that incorporated PGx markers that clinicians could use to assess the risk of OUD. The study included 137 individuals with OUD and 669 individuals without OUD. The researchers evaluated genetic variants in *OPRM1,* A118G, rs1799971, *COMT*, G472A, rs4680, and *CYP2D6*. The *OPRM1*-AA genotype and *CYP2D6* poor and ultrarapid metabolizers were determined to have acceptable diagnostic accuracy (sensitivity, 0.82; specificity, 0.85), goodness of fit ($p = 0.87$), and discrimination (0.89) when considered along with three additional predictors, including age, work disability, and oral morphine equivalent daily dose. Those with OUD were found to have lower incomes; were 10 years younger, on average, than those without OUD; and had more sleep disturbances, more frequent use of benzodiazepines, and a greater likelihood of a history of substance use disorder. Based on these results, the authors concluded that polymorphisms related to *OPRM1* variants and *CYP2D6* phenotypes may be associated with a higher risk of OUD, along with known risk factors such as elevated morphine equivalent daily dose, lower incomes, and age. Additional research that includes high-quality clinical trials is required to establish an accurate and useful clinical predictive model for use in individuals with CNCP who may need long-term use of opioid analgesics.

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Kraus et al. (2024) investigated the use of preoperative PGx testing as it relates to postoperative pain control in participants who were undergoing total knee arthroplasty (TKA) in a recent randomized trial. A total of 68 participants who were aged 18 to 80 years, all of whom were scheduled to undergo primary TKA under general anesthesia, met the inclusion criteria and were evaluated in the study. All participants underwent PGx testing and were then randomly assigned to either the experimental group (n = 38) or control group (n = 30). Prior to surgery, PGx test results for the experimental group were examined by a pharmacist who made recommendations for perioperative medications. In addition, clinically relevant drug-gene interactions were reviewed by a pharmacist, and recommendations specific to drug and dose were made based on CPIC guidelines. Participants were blinded to their PGx test results. Results of PGx tests in participants in the control group were not considered prior to surgery, and standard institutional pathways were followed. Outcomes were measured using the Overall Benefit of Analgesia Score 24 hours after surgery. The secondary outcomes were mean 24-hour pain score, total morphine milligram equivalent (MME), and frequency of opioid administration. No differences were found between the two groups in terms of mean Overall Benefit of Analgesia Score (mean ±SD, 4.7 ±3.7 in the control group vs 4.2 ±2.8 in the experimental group; mean difference, 0.5; 95% CI, -1.1 to 2.1; p = 0.55), total opioids administered, opioid prescribing patterns, or use of tramadol (41% vs 71%; proportion difference, 0.29; 95% CI, 0.05-0.53; nominal p = 0.02; adjusted p > 0.99). Although this study was small, the results suggest that the use of PGx testing in individuals who are undergoing TKA does not lead to better pain management or decreased use of opioid analgesics. The authors recommended future study, with a greater focus on at-risk populations or individuals who are undergoing complex and especially painful surgeries, to determine if PGx testing may be helpful in specific scenarios.

Agulló et al. (2023) conducted a double-blinded RCT to assess the safety and effectiveness of PGx-guided opioid therapy by examining clinical changes in participants with CNCP after 3 months of treatment with opioid analgesics. CPIC clinical recommendations for *CYP2D6* phenotypes and *OPRM1* and *COMT* genotypes were the basis for the PGx-guided treatment used in this study. The trial randomized 60 participants with chronic pain into two arms, both of which were prescribed opioids. The first was guided by *CYP2D6* and *OPRM1* and *COMT* genotypes, and the other received routine care. Participants were interviewed at a baseline visit to assess physical status and medical history. Over the course of the 3-month trial, 10 participants were excluded for various reasons; a total of 50 participants completed the full 3-month trial and follow-up. Data were collected with validated scales and questionnaires, which were self-administered in the presence of an expert clinician. In the group that was guided by genotype, pain intensity was reduced (76 vs 59 mm; p < 0.01), pain relief was improved (28 vs 48 mm; p < 0.05), quality of life was improved (43 vs 56 mm; p < 0.001), incidence of clinically relevant adverse effects was reduced [3 (1-5) vs 1 (0-2); p < 0.01], and opioid dose was reduced by 42% [35 (22-61) vs 60 (40-80) mg/day; p < 0.05] compared with those in the usual prescribing group. The score for health utility was significantly higher in the genotype-guided group due to improving symptoms of sleepiness and depression, and a substantial reduction (30%-34%) was observed in headaches, nervousness, dry mouth, and constipation. The authors proposed that these results support the safety and efficacy of the use of genotype-guided CNCP opioid use for both pain and associated psychiatric disorder management. However, the study was limited by its small sample size from a single pain unit during the COVID-19 pandemic. In addition, the opioid fentanyl was only used in the control arm, creating difficulty in evaluating specific effects of guided treatment due to differences in the drugs between groups. Lastly, participants were on other medications for additional pathologies, which could have contributed to the differences in outcomes. Additional high-quality studies, with larger and more diverse populations, are recommended.

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

Hamilton et al. (2022) conducted a prospective RCT that included 107 participants who were undergoing hip or knee arthroplasty to determine whether PGx testing may be used to effectively customize postoperative pain management after a total joint replacement . PGx testing was performed using a panel of 16 genes, including *CYP2D6, CYP2C9, OPRM1*, and *CYP1A2*, which have an impact on the 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 that these

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drugs would not be normally metabolized were found via PGx testing, alternative drugs (e.g., hydromorphone, meloxicam) were prescribed. Participants recorded pain levels and medications used for 10 days following surgery, and the medication used was converted to MME. The researchers found that genetic variations that impacted medication effects in the standard pain management protocol occurred in 22.4% of participants. The 10-day MME in the control group in those participants who had genetic variants was 162.6 mg. In the custom group, participants with variants and custom medications used only 86.7 mg in the same time frame. 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, participants who were undergoing hip or knee arthroplasty had better pain control and reduced consumption of pain medication; however, they acknowledged that this study was small, especially since the genetic variations of greatest interest are rare.

Rodriguez et al. (2021) conducted a systematic review and examined the efficacy and safety of opioid therapy guided by PGx testing. Of 3,794 records found, five met the 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 of the *CYP2D6* phenotype. The authors concluded that evidence of the safety and efficacy of using PGx testing to guide intervention in opioid therapy for chronic and postoperative pain is very limited.

Hayes (2020; updated 2023) published a Clinical Utility Evaluation of PGx testing related to OUD. Hayes found insufficient evidence to either predict the risk of opioid dependence or improve outcomes in individuals with OUD. In addition, a Hayes Clinical Utility Evaluation (2019a; updated 2022) found limited, low-quality evidence addressing PGx testing prior to prescribing codeine, tramadol, and general opioids related to improved opioid-related treatment outcomes in adult individuals with pain. Lastly, another Hayes (2019b; updated 2022) Clinical Utility Evaluation found insufficient evidence to support or refute the clinical utility of *OPRM1* or *COMT* genotyping for improving pain management in individuals with organic causes of pain.

Muriel et al. (2019) conducted a 6-month, observational, prospective study on the use of PGx testing in 88 participants who were 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; other parameters that were tracked included opioid rotation or discontinuation, adverse drug events, and suspected ADRs. Genotyping consisted of the following genes and variants using reverse transcription polymerase chain reaction: *OPRM1* (A118G), *ABCB1* (C3435T), *COMT* (G472A), *OPRD1* (T921C), and *ARRB2* (C8622T). Five participants were lost to follow-up. Overall, 64% of the remaining participants were female, and 100% were Caucasian. At the baseline visit, a median of six adverse events were recorded, including dry mouth, constipation, sleep disruption, and depression. No difference in ADRs from baseline through the final visits was recorded. Overall, 1,659 ADRs were reported in 359 visits in 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 participants who were AA at that A118G locus having, on average, two or more ADRs than AG/GG participants. Nausea and other gastrointestinal ADRs followed this same pattern. *COMT* genotyping was similar, with AA/GG participants having more ADRs; those who 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 the end of the study. Antidepressants can have similar ADRs to opioids; this may be a confounding variable. The authors found value in PGx testing as a predictor of who may experience nausea and gastrointestinal discomfort, highlighting the potential promising use of PGx in opioid management.

Rheumatoid Arthritis

The body of evidence supporting the PrismRA test is limited. For this test to be considered proven with clinical utility, additional larger and independent studies, with better study designs, are necessary.

Anti–tumor necrosis factor (TNF) medications are the first tier of rheumatoid arthritis (RA) treatment therapy in over 90% of biologic-naive individuals with disease that is not controlled by conventional disease-modifying antirheumatic drugs (DMARDs); 70% of these individuals with RA 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 individual with RA may not respond to traditional anti-TNF therapy before treatment is initiated. Overall, 23 different assessments are made by PrismRA; the resulting biomarker panel includes 19 gene expression features, anticyclic citrullinated protein, and three clinical metrics (sex, body mass index, and patient disease assessment), which stratify individuals based on the likelihood of inadequate response to anti-TNF therapies. Scipher Medicine predicts that a 40% increase in response to the first targeted DMARD could have been achieved for individuals with RA using PrismRA and that both responders and nonresponders have a greater chance of responding to their first biologic/targeted treatment. (Mellors et al., 2020)

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Xie et al. (2026) conducted a prospective interventional cohort study that evaluated the effectiveness of PrismRA testing to guide selection of TNF inhibitor (TNFi) vs non-TNFi biologic or targeted synthetic DMARD therapy in adults with RA. Eligible participants were aged 18 years or older; met 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology criteria; had moderate to high disease activity [Clinical Disease Activity Index (CDAI) > 10], with at least two swollen and tender joints; and had no prior exposure to non-TNFi biologic and targeted synthetic DMARDs (b/tsDMARDs). The PrismRA cohort (n = 330) was compared with a propensity score–matched external comparator cohort (n = 990) drawn from a rheumatology electronic health record database, with weighted logistic regression used for dichotomous outcomes and last observation carried forward imputation for missing data. The primary end point was achievement of a minimal important difference in CDAI at 24 weeks, defined as improvement of ≥ 6 for moderate and ≥ 12 for high baseline disease activity. At 24 weeks, 63.0% of PrismRA participants and 42.4% of comparators achieved the CDAI minimal important difference (OR, 2.31; 95% CI, 1.79-2.99; p < 0.001). The authors concluded that PrismRA-guided treatment selection was associated with significantly better CDAI outcomes than matched external comparators, which supports the use of PrismRA molecular signature response classifier (MSRC) testing to improve clinical outcomes in individuals who require b/tsDMARD therapy. A key limitation is the restricted access to certain b/tsDMARDs imposed by payer policies, which may hinder the practical implementation of the PrismRA MSRC in clinical settings.

Curtis et al. (2024) evaluated the impact of an MSRC on rheumatologists' treatment decisions for individuals with RA by surveying physicians to determine whether MSRC test results influenced their selection of b/tsDMARDs. Data from the Study to Accelerate Information of Molecular Signatures, which was a longitudinal, prospective database of individuals with RA and their MSRC results, were used in this evaluation. The rate of b/tsDMARD prescriptions that demonstrated alignment with MSRC results and the total percentage of providers using MSRC results to guide treatment were also included in the results. In total, 1,018 individuals were included in the analysis, and of them, 70.7% (720 of 1,018) received MSRC results prior to treatment selection. Of the 720, 544 (75.6%) were prescribed a b/tsDMARD that aligned with their MSRC results; 84.6% of the prescribing physicians reported that they had used the MSRC results to direct the choice of treatment. For those who did not align choice of treatment with MSRC results, the most common reason provided was concerns with health insurance coverage. The researchers determined that the MSRC test appears to provide helpful information for making treatment decisions in regard to individuals with RA but noted limitations, including the use of a survey, which may have been impacted by individual biases and differences in treatment practices across various regions of the country. The study was funded by the manufacturer of an MSRC test, which introduces additional potential for bias. In addition, potential step-therapy treatments required by insurers were not accounted for in this study. The authors recommended long-term studies that further clarify how MSRC testing is used by treating providers.

A Hayes (2022b; updated 2025) Molecular Test Assessment evaluated the clinical validity, utility, and analytic validity of Scipher Medicine'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 the use of the PrismRA test. Additional studies that evaluate PrismRA in larger and more diverse populations are needed. A 2025 update to the initial assessment indicates that although new studies have been published since the 2022 assessment, the rating of D2 is unlikely to change based on these publications.

Curtis et al. (2022) compared a group of individuals (n = 627), who had been tested using an MSRC, with a control group; the study used propensity score matching, which was applied to balance baseline traits. The individuals in the MSRC-tested group were participants in the Study to Accelerate Information of Molecular Signatures, while the control group members (n = 2,721) were external; information was obtained from a large, deidentified database of U.S. electronic health records. All individuals either began a b/tsDMARD or continued anti-TNF therapy. The researchers calculated ORs for 6-month response based on CDAI scores for low disease activity/remission (CDAI-LDA/REM), remission (CDAI-REM), and minimally important differences (CDAI-MID). In the group of MSRC-tested individuals, a nonresponse signature was obtained in 59% of the group, and MSRC-aligned treatment was provided in 70% of the group. In individuals who were treated with anti-TNF therapy, the MSRC had a positive predictive value of 88% and sensitivity of 54%. Those individuals who received MSRC-guided treatment were significantly more likely to respond to b/tsDMARDs than individuals who received standard care [CDAI-LDA/REM: 36.0% vs 21.9%, OR, 2.01 (1.55-2.60); CDAI-REM: 10.4% vs 3.6%, OR, 3.14 (1.94-5.08); CDAI-MID: 49.5% vs 32.8%, OR, 2.01 (1.58-2.550)]. Based on these results, the authors asserted that the clinical validity of the MSRC test supports high clinical utility since treatment that was guided by MSRC testing led to substantially better outcomes than standard care, with almost three times more individuals reaching CDAI remission. However, some limitations were noted, including the intrinsic limitations in the ability to identify unmeasured confounders in an external control group and the length of time that passed from the baseline assessment and MSRC testing to the beginning of treatment in some members of the MSRC-tested group (up to 1 year). In addition, several authors had

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associations with the corporation that manufactures the MSRC test that was used and funded the study, which creates a potential for bias.

Jones et al. (2021; included in the 2022b Hayes report) conducted a nonrandomized retrospective assay to assess the analytic and clinical validity of the PrismRA test in patients with RA who have not responded to TNF-α inhibitor (TNFi) therapy. Overall, 174 individual samples from the NETWORK-004 clinical study were analyzed for clinical validity. Of these, 100 had not undergone any targeted RA therapy, and 74 had been exposed to a TNFi. The test results classified samples according to nonresponse 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 the 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 nonresponse signatures in individuals with RA accurately and reproducibly. Limitations to this study include a lack of randomization, a small population, wide CIs, and an inability to determine the potential for selection bias due to lack of information regarding the original NETWORK-004 study.

Strand et al. (2022), also included in the Hayes (2022b) report, conducted a prospective cohort study to assess provider decision-making and treatment outcomes following the use of the PrismRA test to guide the selection of b/tsDMARDs for participants with RA. In the decision-making cohort, 377 participants met the inclusion criteria and were evaluated according to treatment, treatment modifications, and physician questionnaire responses. For the clinical outcomes cohort, 212 participants completing a 12-week follow-up visit and a subset of 85 participants 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 reported 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. Of participants who were prescribed a b/tsDMARD consistent with their PrismRA test results, the 24-week mean ACR criteria for ≥ 50% improvement (ACR50) responses were 39.6%. Participants whose test results indicated nonresponse had significantly improved responses to non-TNFi therapies compared with TNFi therapies (ACR50, 34.8% vs 10.3%; p = 0.05), indicating that predicted nonresponders to TNFi therapies were not nonresponders to other types of RA therapy. The researchers concluded that incorporating PrismRA into individuals' care could significantly improve RA treatment outcomes; however, the study was nonrandomized and nonblinded, and no comparison group of impacted participants who did not undergo testing with the PrismRA test was included. Racial diversity was also limited (79%-84% of the study population was White), and significant differences in characteristics, such as age, were observed between the groups. Lastly, there is potential for bias related to affiliations with the test laboratory. Longer-term data are required to evaluate persistence and treatment patterns, along with disease burden.

Mellors et al. (2020) reported on the Scipher Medicine cross-cohort, cross-platform study that developed the molecular test to predict decreased response/nonresponse (ACR < 50) to anti-TNF therapies in biologic-naive participants with RA using the Human Interactome model; 39 RA-associated SNPs were evaluated. Data taken from two cohorts collected from the CERTAIN (Comparative Effectiveness Registry to Study Therapies for Arthritis and Inflammatory Conditions) trial (n = 58/participant discovery cohort; n = 143/training cohort) were evaluated to produce a drug biomarker panel; laboratory studies included complete blood cell count, C-reactive protein level, rheumatoid factor titer, and anticitrullinated protein level. A validation cohort (n = 175) was matched to the training cohort for response rate, age, and gender, and all participants in the validation cohort from the CERTAIN study had a CDAI of > 10. The results revealed that the biomarker panel identified nonresponders with an 89.8% positive predictive value 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 nonresponsiveness show promise for advancing precision medicine treatment for RA and other complex autoimmune conditions for which individuals have 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 biological treatment. They observed clinical decision-making for 175 individuals enrolled in the CERTAIN study who received anti-TNF treatment after not responding to a conventional synthetic DMARD and modeled clinical decision-making for the same cohort using PrismRA. In total, 69.7% of individuals did not reach ACR50 in response to anti-TNF treatment. A PrismRA score of ≥ 11.8 was used to identify individuals with a high or very-high likelihood or poor response/nonresponse to an anti-TNF treatment. Overall, 68 individuals were predicted to be poor responders: 61 were correctly predicted, and seven were misclassified, as they did reach ACR50. With the first treatment strategy, 70% of individuals did not reach ACR50 within 6 months. Subsequently, these individuals received second-line treatment, which was either a second anti-TNF treatment (60%) or an alternate treatment (40%); these individuals had a 20% ACR50 response within 12 months. Individuals who reached ACR50 in the first 6 months stayed on therapy for the entire 12 months. Overall, 44% of individuals in the 175-individual cohort were

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predicted to have achieved ACR50 within the first 12 months of treatment. With the second strategy using PrismRA, the 68 individuals who were poor responders were assigned to another treatment therapy; 27 reached ACR50 in the first 6 months, and the other 107 were prescribed an anti-TNF treatment. Of 107 responders, 61 did not reach ACR50 and were given a treatment with another mechanism of action as a second-line therapy; 16 of 61 then achieved ACR50. Therefore, 57% of individuals from the 175-individual cohort were predicted to reach ACR50 within the first 12 months of treatment. The researchers listed multiple limitations of this study, including the lack of a sensitivity analysis and assumption that health care providers will follow the PrismRA test results with full adherence. The authors concluded that precision medicine and biomarker-driven treatment are a necessary step toward advancing the clinical effectiveness of and cost savings for all medications, including treatment for individuals with RA.

Johnson and Weinblatt (2018) introduced the PrismRA test for Scipher Medicine, stating that it predicts nonresponse 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 of 92% and true negative rate of 50%. Validation of the predictive accuracy of PrismRA in a clinical trial is ongoing. Scipher Medicine is in communication with rheumatologists and payers to determine optimal clinical end points. Once the end points from the trial are determined, PrismRA will be offered commercially as a College of American Pathologists–proficient, Clinical Laboratory Improvement Amendments–certified laboratory study. PrismRA will allow more individuals with RA to achieve good response/remission (ACR50), resulting in improved outcomes in individuals and significant cost savings, according to the authors.

Other Pharmacogenetic Multigene Panel Testing

The evidence for the use of PGx multigene panel testing to guide individualized therapies for indications such as multimorbidity, polypharmacy, cancer treatment toxicity, medication response, and inflammatory bowel disease (IBD) and for general use with medication prescription is insufficient at this time since clinical efficacy has not been substantiated in the scientific literature.

Garrison et al. (2025) conducted a retrospective electronic health record review in 99 children and adolescents with autism spectrum disorder who were treated in partial hospitalization or intensive outpatient programs, comparing those who received PGx testing with those receiving TAU. The coprimary outcomes were polypharmacy and PQ-LES-Q (Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire) scores, and no significant differences were found between groups in polypharmacy ($p = 0.938$ at admission; $p = 0.227$ at discharge) or PQ-LES-Q scores ($p = 0.664$ at admission; $p = 0.805$ at discharge), with both groups improving similarly from low to average life satisfaction. The authors concluded that incorporating PGx testing into the medical workup did not improve outcomes, with similar polypharmacy and quality of life across treatment groups and no benefit in clinical outcomes observed when assessing congruency, polypharmacy, quality of life, symptom severity, or other variables. There are limitations, including the retrospective design, which restricted understanding of how PGx results were used in prescribing decisions and made medication adherence dependent on self-report and refill data, while prior failed medication trials were not assessed. Key limitations include a modest sample size that may have reduced statistical power and a short average length of stay that limited the ability to detect medication-related changes. Measurement limitations include the use of pediatric assessment tools for patients who were up to age 20 years; lack of evaluation of communication and sensorial disorders; and absence of systematic assessment of adverse effects. Additional limitations involve uncertainty in interpreting how specific enzyme variants influence safety and efficacy for drugs with multiple active moieties; complexity of multifactorial prescribing decisions; and restricted generalizability because only psychotropic medications were analyzed.

Leong et al. (2025) conducted a large-scale PGx analysis using data from the 100,000 Genomes Project, focusing on individuals with cancer. The study evaluated the potential clinical utility of reporting germline PGx variants that are known to influence drug-induced toxicity. Specifically, the researchers analyzed whole-genome sequencing data from 76,805 individuals, linking it with medical records to assess clinical outcomes. Focus was placed on four key genes: *DPYD*, *NUDT15*, *TPMT*, and *UGT1A1* (14 PGx variants). These genes are associated with toxicity from five commonly used cancer drugs: capecitabine, fluorouracil, mercaptopurine, thioguanine, and irinotecan. A phenome-wide association study was then performed to determine whether phenotypes suggestive of ADRs were more common in drug-exposed individuals in whom relevant PGx variants were identified. For a subset of 7,081 individuals with cancer, PGx variant data for *DPYD* were collected and reported back to clinicians; clinical outcomes were also collected. The analysis revealed clinically relevant PGx variants across the four relevant genes in 62.7% of individuals. Based on national prescription data (in England), the authors estimated that approximately 14,540 individuals per year may have the potential to benefit from dose adjustments or alternative therapies (based on PGx results) to reduce ADR risk. A significant association between PGx variants in *DPYD* and toxicity-related phenotypes was also identified in individuals who were treated with capecitabine or fluorouracil specifically. Overall, the authors proposed that the integration of PGx testing into routine cancer care may provide helpful information in terms of guiding prescribing, with a goal of reducing the risk of ADRs. Although the results are promising, several limitations exist. The study was retrospective, which may introduce biases related to data completeness and accuracy. Also, since the study only focused on four genes and five drugs, other

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relevant PGx interactions may have been missed. In addition, some PGx variants may have uncertain significance clinically, and the impact may also vary across populations. Lastly, the study does not represent ethnic diversity, limiting the generalizability of variant/drug associations. Further comprehensive study of PGx testing in individuals with cancer across diverse populations via well-designed trials is needed to support integration of this technology into standard clinical care.

Lingaratnam et al. (2024) conducted a systematic review and meta-analysis to assess the safety outcomes related to the use of PGx-directed treatment options (analysis 1) and sought to identify promising genomic variants with the potential to predict medication toxicity and severity of symptoms in individuals with cancer diagnoses who had undergone active cancer treatment (analysis 2). The primary end points included severe adverse effects (SAEs) or pain and vomiting, as defined by specific trial procedures and evaluated by trial investigators. A total of six studies met the inclusion criteria and were evaluated in analysis 1; these studies included PGx-guided dosing related to treatment with fluoropyrimidines, irinotecan, and a combination of multiple medications, incorporating both anticancer and supportive care. The most frequently studied genes were *MTHFR, UGT1A1, ABCB1, TYMS, UGT1A6/UGT1A7/UGT1A9, and HLA-DRB1*. Overall, 40 studies were included in a subset analysis (analysis 2). The reviewers found a lower absolute occurrence of SAEs with evidence-based PGx-guided treatment approaches than with TAU (16% vs 34%, respectively; RR, 0.72; 95% CI, 0.57-0.91; p = 0.006; I^2 = 34%) in meta-analysis 1. In meta-analysis 2, nine variant pairs of interest were detected, including the genes *TYMS, ABCB1, UGT1A1, HLA-DRB1*, and *OPRM1*. The authors concluded that the use of PGx testing led to a reduction in the rates of SAEs in individuals with cancer who were undergoing treatment based on the outcome of this analysis. The identification of emerging genetic variations warrants further study that is focused on the development and improvement of PGx testing for individuals who are undergoing cancer treatment and on the safety of supportive care treatments. High-quality clinical trials are recommended, which should evaluate emerging pharmacogenes (including those identified by this review) and their relationship not only to anticancer treatment but to efficacy outcomes as well.

Swen et al. (2023) reported that the use of PGx testing for specific GDIs has been studied in several RCTs, with evidence for improved outcomes, although robust evidence related to PGx panel testing remains relatively limited; they published the results of an open-label, cluster-randomized, controlled, multicenter trial of a 12-gene PGx panel (the PREPARE study). The trial took place in multiple clinical settings across seven European countries and included participants with a broad range of diseases and medication needs. Overall, 39 drugs were used to treat multiple conditions in PREPARE. Although the trial initially enrolled 6,944 participants, who were assigned to receive either PGx-guided treatment (n = 3,342) or TAU (n = 3,602), 751 of them either withdrew consent or were lost to follow-up. Of the remaining participants, 1,558 were found to have an actionable test result related to the drug that they were being prescribed; of these participants, a clinically significant ADR transpired in 21% (152 of 725) in the experimental group and 27.7% (231 of 833) in the control group (OR, 0.70; 95% CI, 0.54-0.91; p = 0.0075). In the entire population, the incidence of ADRs was 21.5% of 2,923 experimental group participants and 28.6% of 3,270 control group participants. The most common study drug linked to actionable variant findings was atorvastatin (n = 716); clopidogrel (n = 619) and tacrolimus (n = 472) also had a significant number of participants with associated variants identified. The volume and severity of ADRs varied per country, which may have been related to the type of facility from which participants were recruited (i.e., cancer clinic vs primary care). Based on these results, the authors asserted that the use of the 12-gene PGx panel test to guide treatment selection substantially decreased the incidence of ADRs in a diverse population of participants in European health care settings and affirmed that their findings bolster the existing evidence that supports broad use of panel-based PGx testing for improved safety of drug therapy. They highlighted the potential benefit of standardizing a validated PGx testing system for decision-making support related to medication prescription. The study does have noted limitations; these include subjective, participant-reported ADRs (although the assessment was independently validated in 10% of participants who were randomly selected), reliance on participants to contact the research team if a secondary drug was used, and low volumes of participants for some of the drugs included in the study, some of which had high-toxicity profiles (e.g., mercaptopurine, azathioprine, thioguanine). This study focused only on reduction of adverse effects. Another area requiring further evaluation is the impact of PGx panel testing on drug efficacy. In addition, 97.7% of participants were of European, Mediterranean, or Middle Eastern ancestry. Additional studies that incorporate greater ethnic diversity are required before this test can be widely recommended.

Plaza et al. (2024) performed a systematic review that investigated the status of evidence specific to genetic variants that are associated with biological agent therapy in IBD, contending that PGx is an emerging area of importance for the optimization of IBD treatment. In total, 28 studies were included in the review. In addition, the Pharmacogenomics Knowledge Base (PharmGKB) was used to gather evidence on the relationship between known genetic variants and IBD treatment. The researchers indicated that GWASs have detected SNPs that have a potential relationship with the pathogenesis of IBD. Several studies have also shown a relationship between SNPs and pharmacological response to IBD treatments. The review indicates that the most important SNPs related to biological therapeutics are those linked to immunity, such as immunorecognition and cytokine production. The authors stressed the importance of large, high-quality

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studies that are designed to investigate the relationship of PGx and biological therapy, which will hopefully lead to the ability to determine the most valuable SNP assessment for incorporation into IBD treatment.

In a 2022 systematic review, O'Shea et al. sought to establish the efficacy of multigene, multidisease, and multidrug PGx interventions in adults with multiple morbidities and/or prescription polypharmacy in health care settings and to inform the enactment of PGx-guided treatments in practice. The review included 12 studies that assessed multimedicine PGx in individuals with multiple morbidities or polypharmacy and that reported on relevant core outcomes. Studies varied in design and quality; six noncomparative 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 the benefits for individuals or health systems could be made based on this review. They asserted that there is promise for individualizing therapies through PGx guidance, but further high-quality studies across differing care settings are required to establish efficacy.

David et al. (2021) conducted a systematic review and meta-analysis that evaluated the current evidence regarding the impact of PGx testing on hospital admissions and whether PGx leads to changes in medication. Five studies that were focused on hospitalization and five studies that were focused on medication change were identified for evaluation. The 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 the TAU comparator arm. The researchers believe that these results show proof of concept for the use of PGx in prescribing that may lead to benefit in individuals but point out the evidence gaps that exist related to the introduction of PGx into health care systems. They feel that their analysis will assist with identifying areas in which further research is needed, including investigation of the perspectives of health care providers and individuals to assist in the design of patient-centric PGx-guided care.

Clinical Practice Guidelines

American Academy of Child and Adolescent Psychiatry (AACAP)

In a 2020 policy statement, the AACAP outlines the limitations in published studies that address the use of combinatorial PGx tests to guide medication choice and dosing (in adults), including potential conflicts of interest, small sample sizes, limited duration of follow-up, and appropriate control groups and blinding. In addition, the AACAP notes that "pharmacogenetic testing provides little meaningful information when two or more medications are used concurrently." The policy statement ultimately recommends that:

- Clinicians should avoid the use of PGx testing to select psychotropic medications in children and adolescents.
- Future high-quality, prospective studies to assess the clinical significance of pharmacodynamic and combinatorial PGx testing in children and adolescents should be undertaken.

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 the management of RA.

The ACR has identified 11 measures of disease activity for RA 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), 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), and 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 (≥ 50% improvement) or 70 (≥ 70% improvement) 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)

The CPIC is an international organization, with membership that includes clinicians, scientists, laboratorians, and other PGx experts, with the purpose of facilitating the use of PGx test results for patient care. The CPIC's goal is to address the barrier caused by difficulty translating genetic laboratory test results into actionable prescribing decisions for applicable

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drugs by creating freely available, peer-reviewed, evidence-based, and updatable gene/drug CPGs. The CPIC started as a shared project between the Pharmacogenetics Research Network and the PharmGKB in 2009. CPIC guidelines are indexed in PubMed as clinical guidelines, endorsed by the American Society of Health-System Pharmacists and the American Society for Clinical Pharmacology & Therapeutics, and are referenced in ClinGen and PharmGKB. (CPIC, 2024)

In an updated guideline (Bousman et al., 2023), the CPIC expanded on their existing guideline for *CYP2D6* and *CYP2CD19* genotypes and selective serotonin reuptake inhibitor (SSRI) antidepressant dosing and summarized the effect of *CYP2D6*, *CYP2C19, CYP2B6, SLC6A4*, and *HTR2A* genotypes on the dosing, efficacy, and tolerability of antidepressant medications. The guideline states that *CYP2D6*, *CYP2C19*, and/or *CYP2B6* genotype results may be beneficial for detecting patients who are at a higher risk of either ADRs or inadequate response to SSRI therapy based on moderate- to high-quality evidence. Risks have been identified, including the potential to miss the identification of rare or new variations that are usually not tested on current platforms. In such cases, the actual phenotype may be different from the predicted phenotype. Other factors, such as age, diet, comorbidities, smoking, pregnancy, concomitant medications, and epigenetic variation, may also apply. The CPIC did not provide recommendations for *HTR2A* and *SLC6A4* because the evidence supporting an association between these genotypes and SSRI antidepressants is mixed/insufficient to support clinical validity and utility at this time (CPIC level C: no recommendation). CPIC guidelines (Hicks et al., 2016; updated 2019) also address the use of *CYP2D6* and *CYP2C19* genotyping for dosing of tricyclic antidepressants (moderate- to high-quality evidence).

No existing CPIC guidelines provide recommendations regarding the use of multigene panels that include testing of five or more genes.

European Alliance of Associations for Rheumatology (EULAR)

Smolen et al. (2022) updated the EULAR recommendations for the management of RA based on evidence from three systematic literature searches on the safety and efficacy of DMARDs and glucocorticoids. The EULAR task force provided five principles and 11 recommendations regarding the use of conventional synthetic DMARDs, glucocorticoids, and b/tsDMARDs. Neither the use of MSRCs nor PrismRA was discussed, but one of the items on the EULAR research agenda is identification of new biomarkers to help stratify patients with RA and predict therapeutic response or lack of response.

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 antidepressant and antipsychotic medications. They indicated that the evidence also supports additional testing for human leukocyte antigen genes with the 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. This review noted that PGx testing is not regulated at present and that many tests are available 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 that supports 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 that this testing will ultimately become an important tool for use in patients with psychiatric disorders.

The ISPG updated its statement on genetic testing in 2019. Its recommendation regarding PGx testing is as follows: “Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care. We recommend HLA-A and HLA-B testing prior to the use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic 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®)

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for adult cancer pain (v1.2026) include a section on principles of PGx, which indicates that PGx testing may be considered before initiation of treatment or during treatment

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of pain when concerns of toxicity or a lack of analgesic response is present or suspected. The use of PGx panel testing is not addressed.

Standardizing Laboratory Practices in Pharmacogenomics (STRIPE) Collaborative Community

To provide an overview of the current state of recommendations specific to PGx testing in existing U.S. CPGs, a clinical subcommittee of the STRIPE Collaborative Community Study Designs Task Force, comprising experts in PGx testing, was formed. This group identified gene-drug pairs with published CPIC guidelines or those included in the U.S. Food and Drug Administration table of PGx associations and then reviewed gene-drug pairs that are addressed in current U.S.-based CPGs (Hertz et al., 2024). Overall, 21 gene-drug (or drug class) pairs, with well-established associations, were identified and categorized into five therapeutic areas (cardiology, pain/general medicine, infectious disease, psychiatry/neurology, and oncology). All 21 pairs had evidence of clinical actionability according to the CPIC. The experts found that relatively few CPGs in the U.S. provide recommendations specific to PGx testing, and recommendations for the same gene-drug pairs often vary between organizations, sometimes even between different CPGs from the same organization. No information regarding panel tests that include five or more genes is provided in this review. The subcommittee concluded that additional effort, both in the STRIPE Collaborative Community Study Designs Task Force and other organizations, is required to (1) develop a standardized approach to analyzing evidence related to the clinical utility of PGx to provide clear PGx recommendations in CPGs and (2) direct study designs that will provide this evidence.

U.S. Department of Veterans Affairs/Department of Defense (VA/DOD)

In a 2022 joint CPG for the management of MDD (McQuaid et al.), a VA/DOD multidisciplinary work group addressed the use of PGx testing to guide the selection of antidepressant agents in patients with MDD. The work group advised that evidence to recommend either for or against the use of PGx testing in this setting was insufficient.

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 Act of 1988. More information is available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm. (Accessed June 4, 2026)

The list of genetic tests that have been cleared or approved by the FDA Center for Devices and Radiological Health is available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed June 4, 2026)

A full list of FDA-approved or -cleared companion diagnostics is available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. (Accessed June 4, 2026)

A table of pharmacogenetic associations is available from the FDA at: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. (Accessed June 4, 2026)

References

Aboelbaha S, Zolezzi M, Elewa H. Effect of pharmacogenetic-based decision support tools in improving depression outcomes: a systematic review. Neuropsychiatr Dis Treat. 2021 Jul;17:2397-2419.

Agulló L, Aguado I, Muriel J, et al. Pharmacogenetic guided opioid therapy improves chronic pain outcomes and comorbid mental health: a randomized, double-blind, controlled study. Int J Mol Sci. 2023 Jun;24(13):10754.

Albers RE, Dyer MP, Kucera M, et al. Meta-analysis of response and remission outcomes with a weighted multigene pharmacogenomic test for adults with depression. J Clin Psychopharmacol. 2025 Nov-Dec;45(6):570-579.

American Academy of Child and Adolescent Psychiatry. Clinical use of pharmacogenetic tests in prescribing psychotropic medications for children and adolescents [Internet]. Washington (DC): AACAP; 2020 Mar. Available at: https://www.aacap.org/AACAP/Policy_Statements/2020/Clinical-Use-Pharmacogenetic-Tests-Prescribing-Psychotropic-Medications-for-Children-Adolescents.aspx. Accessed June 3, 2026.

Annis AC, Gunaseelan V, Smith AV, et al. Genetic associations of persistent opioid use after surgery point to OPRM1 but not other opioid-related loci as the main driver of opioid use disorder. Genet Epidemiol. 2025 Jan;49(1):e22588.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

Baum ML, Widge AS, Carpenter LL, et al.; American Psychiatric Association (APA) Workgroup on Biomarkers and Novel Treatments. Pharmacogenomic clinical support tools for the treatment of depression. Am J Psychiatry. 2024 Jul;181(7):591-607.

Bergman MJ, Kivitz AJ, Pappas DA, et al. Clinical utility, and cost savings in predicting inadequate response to anti-TNF therapies in rheumatoid arthritis. Rheumatol Ther. 2020 Dec;7(4):775-792.

Billings J, Racsa PN, Bordenave K, et al. The impact of real-world cardiovascular-related pharmacogenetic testing in an insured population. Int J Clin Pract. 2018 Jun;72(6):e13088.

Borobia AM, Dapia I, Tong HY, et al. Clinical implementation of pharmacogenetic testing in a hospital of the Spanish National Health System: Strategy and experience over 3 years. Clin Transl Sci. 2018 Mar;11(2):189-199.

Bousman CA, Arandjelovic K, Mancuso SG, et al. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. Pharmacogenomics. 2019 Jan;20(1):37-47.

Bousman CA, Bengesser SA, Aitchison KJ, et al. Review and consensus on pharmacogenomic testing in psychiatry. Pharmacopsychiatry. 2021 Jan;54(1):5-17.

Bousman CA, Stevenson JM, Ramsey LB, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A genotypes and serotonin reuptake inhibitor antidepressants. Clin Pharmacol Ther. 2023 Jul;114(1):51-68.

Bradley P, Shiekh M, Mehra V, at al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating clinical utility. J Psychiatr Res. 2018 Jan;96:100-107.

Brown L, Vranjkovic O, Li J, et al. The clinical utility of combinatorial pharmacogenomics testing for patients with depression: a meta-analysis. Pharmacogenomics. 2020 Jun;21(8):559-569.

Brown LC, Stanton JD, Bharthi K, et al. Pharmacogenomic testing and depressive symptom remission: a systematic review and meta-analysis of prospective, controlled clinical trials. Clin Pharmacol Ther. 2022 Dec;112(6):1303-1317.

Bunka M, Wong G, Kim D, et al. Evaluating treatment outcomes in pharmacogenomic-guided care for major depression: a rapid review and meta-analysis. Psychiatry Res. 2023 Mar;321:115102.

Clinical Pharmacogenetics Implementation Consortium (CPIC®). CPIC website [Internet]. Stanford (CA): CPIC. Available at: CPIC (cpicpgx.org). Accessed June 3, 2026.

Curtis JR, Strand V, Golombek S, et al. Patient outcomes improve when a molecular signature test guides treatment decision-making in rheumatoid arthritis. Expert Rev Mol Diagn. 2022 Nov:1-10.

Curtis JR, Strand V, Golombek SJ, et al. Decision impact analysis to measure the influence of molecular signature response classifier testing on treatment selection in rheumatoid arthritis. Rheumatol Ther. 2024 Feb;11(1):61-77.

David V, Fylan B, Bryant E, et al. An analysis of pharmacogenomic-guided pathways and their effect on medication changes and hospital admissions: a systematic review and meta-analysis. Front Genet. 2021 Jul;12:698148.

Del Tredici AL, Johnson HL, DeHart B, et al. Real-world impact of pharmacogenomic testing on medication use and healthcare resource utilization in patients with major depressive disorder. J Clin Psychopharmacol. 2025 Jul-Aug;45(4):320-328.

England BR, Tiong BK, Bergman MJ, et al. 2019 update of the American College of Rheumatology recommended rheumatoid arthritis disease activity measures. Arthritis Care Res (Hoboken). 2019 Dec;71(12):1540-1555.

Escorial M, Muriel J, Agulló L, et al. Clinical prediction of opioid use disorder in chronic pain patients: a cohort-retrospective study with a pharmacogenetic approach. Minerva Anestesiol. 2024 May;90(5):386-396.

Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2021 Jul;73(7):924-939.

Garrison SR, Schweinert SA, Boyer MW, et al. Polypharmacy and pharmacogenomics in high-acuity behavioral health care for autism spectrum disorder: a retrospective study. Child Adolesc Psychiatry Ment Health. 2025 May;19(1):60.

Greden JF, Parikh SV, Rothschild AJ, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. 2019 Jan;111:59-67.

Hamilton WG, Gargiulo JM, Reynolds TR, et al. Prospective randomized study using pharmacogenetics to customize postoperative pain medication following hip and knee arthroplasty. J Arthroplasty. 2022 Jun;37(6S):S76-S81.

Hansson P, Blacker C, Uvdal H, et al. Pharmacogenomics in pediatric oncology patients with solid tumors related to chemotherapy-induced toxicity: a systematic review. Crit Rev Oncol Hematol. 2025 Jul;211:104720.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

Hayes, Inc. Clinical Utility Evaluation. Pharmacogenetic and pharmacogenomic testing for opioid treatment for pain in adults – selected single-gene variants and pharmacogenomic panels. Hayes, Inc.; December 11, 2019a, updated October 26, 2022.

Hayes, Inc. Clinical Utility Evaluation. Pharmacogenetic and pharmacogenomic testing to improve outcomes related to opioid use disorder. Hayes, Inc.; April 27, 2020, updated June 30, 2023.

Hayes, Inc. Clinical Utility Evaluation. Pharmacogenetic testing for attention-deficit/hyperactivity disorder treatment. Hayes, Inc.; January 12, 2022a, updated June 11, 2025.

Hayes, Inc. Clinical Utility Evaluation. Pharmacogenetic testing for opioid treatment for pain – OPRM1 and COMT variants. Hayes, Inc.; December 3, 2019b, updated October 24, 2022.

Hayes, Inc. Clinical Utility Evaluation. Pharmacogenomic testing for major depressive disorder. Hayes, Inc.; May 9, 2025a.

Hayes, Inc. Clinical Utility Evaluation. Pharmacogenomic testing for schizophrenia disorder. Hayes, Inc.; July 29, 2025b.

Hayes, Inc. Molecular Test Assessment. GeneSight Psychotropic (Assurex Health Inc./Myriad Neuroscience). Hayes, Inc.; September 10, 2021, updated September 17, 2024.

Hayes, Inc. Molecular Test Assessment. PrismRA (Scipher Medicine). Hayes, Inc.; April 22, 2022b, updated May 12, 2025.

Hertz DL, Bousman CA, McLeod HL, et al. Recommendations for pharmacogenetic testing in clinical practice guidelines in the US. Am J Health Syst Pharm. 2024 Aug;81(16):672-683.

Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther. 2017 Jul;102(1):37-44.

International Society of Psychiatric Genetics (ISPG) genetic testing statement. Updated 2019. Available at: https://ispg.net/genetic-testing-statement/. Accessed June 16, 2026.

Jethwa S, Ball M, Langlands K. Pharmacogenomic-guided opioid therapy for pain: a systematic review and meta-analysis of randomised controlled trials. Pharmacogenomics J. 2025 Jul;25(4):20.

Johnson K and Weinblatt M. Precision medicine in complex disease: use of the PrismRA test to stratify patients for response to anti-TNF therapy in rheumatoid arthritis. 2018 October. Available at: https://www.mydigitalpublication.com/publication/?m=46092&i=547602&p=44&pp=1&ver=html5. Accessed August 22, 2025.

Jones A, Rapisardo S, Zhang L, et al. Analytical and clinical validation of an RNA sequencing-based assay for quantitative, accurate evaluation of a molecular signature response classifier in rheumatoid arthritis. Expert Rev Mol Diagn. 2021 Nov;21(11):1235-1243.

Jung J, Tawa EA, Muench C, et al. Genome-wide association study of treatment response to venlafaxine XR in generalized anxiety disorder. Psychiatry Res. 2017 Aug;254:8-11.

Kang Z, Qin Y, Sun Y, et al. Multigenetic pharmacogenomics-guided treatment vs treatment as usual among hospitalized men with schizophrenia: a randomized clinical trial. JAMA Netw Open. 2023 Oct;6(10):e2335518.

Kraus MB, Bingham JS, Kekic A, et al. Does preoperative pharmacogenomic testing of patients undergoing TKA improve postoperative pain? A randomized trial. Clin Orthop Relat Res. 2024 Feb;482(2):291-300.

Leong IUS, Cabrera CP, Cipriani V, et al. Large-scale pharmacogenomics analysis of patients with cancer within the 100,000 Genomes Project combining whole-genome sequencing and medical records to inform clinical practice. J Clin Oncol. 2025 Feb;43(6):682-693.

Li L, Xu L, Wang Q, et al. Effectiveness of pharmacogenomic testing across age groups for depressive disorder treatment and its age-dependent effects on cognitive function: a randomized controlled trial. J Affect Disord. 2026 Apr;398:121065.

Lingaratnam S, Shah M, Nicolazzo J, et al. A systematic review and meta-analysis of the impacts of germline pharmacogenomics on severe toxicity and symptom burden in adult patients with cancer. Clin Transl Sci. 2024 May;17(5):e13781.

McQuaid JR, Buelt A, Capaldi V, et al. The management of major depressive disorder: synopsis of the 2022 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. Ann Intern Med. 2022 Oct;175(10):1440-1451.

MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2020 Jun 24]. Pharmacogenetic Tests; [updated 2025 August 7]. Available at: https://medlineplus.gov/lab-tests/pharmacogenetic-tests/. Accessed June 16, 2026.

Proprietary Information of UnitedHealthcare. Copyright 2026 United HealthCare Services, Inc.

Mellors TW, Withers JW, Ameli A, et al. Clinical validation of a blood-based predictive test for stratification of response to tumor necrosis factor inhibitor therapies in rheumatoid arthritis patients. Netw Syst Med. 2020 Jul;3(1):1-14.

Menchón JM, Espadaler J, Tuson M, et al. Patient characteristics driving clinical utility in psychiatric pharmacogenetics: a reanalysis from the AB-GEN multicentric trial. J Neural Transm (Vienna). 2019 Jan;126(1):95-99.

Milosavljević F, Molden PE, Ingelman-Sundberg PM, et al. Current level of evidence for improvement of antidepressant efficacy and tolerability by pharmacogenomic-guided treatment: a systematic review and meta-analysis of randomized controlled clinical trials. Eur Neuropsychopharmacol. 2024 Apr;81:43-52.

Muriel J, Margarit C, Barrachina J, et al. Pharmacogenetics and prediction of adverse events in prescription opioid use disorder patients. Basic Clin Pharmacol Toxicol. 2019 Apr;124(4):439-448.

National Cancer Institute (NCI) Dictionary of Genetics Terms. Multigene test. Available at: https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/multigene-test. Accessed June 11, 2026.

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Adult cancer pain. Version 1.2026.

Ontario Health (Quality). Multi-gene pharmacogenomic testing that includes decision-support tools to guide medication selection for major depression: a health technology assessment. Ont Health Technol Assess Ser. 2021 Aug;21(13):1-214.

O'Shea J, Ledwidge M, Gallagher J, et al. Pharmacogenetic interventions to improve outcomes in patients with multimorbidity or prescribed polypharmacy: a systematic review. Pharmacogenomics J. 2022 Mar;22(2):89-99.

Oslin DW, Lynch KG, Shih MC, et al.; PRIME Care Research Group. Effect of pharmacogenomic testing for drug-gene interactions on medication selection and remission of symptoms in major depressive disorder: the PRIME Care randomized clinical trial. JAMA. 2022 Jul;328(2):151-161.

Pérez V, Salavert A, Espadaler J, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC Psychiatry. 2017 Jul;17(1):250.

Perlis RH, Mehta R, Edwards AM, et al. Pharmacogenetic testing among patients with mood and anxiety disorders is associated with decreased utilization and cost: a propensity-score matched study. Depress Anxiety. 2018 Oct;35(10):946-952.

Plaza J, Mínguez A, Bastida G, et al. Genetic variants associated with biological treatment response in inflammatory bowel disease: a systematic review. Int J Mol Sci. 2024 Mar;25(7):3717.

Ratner L, Zhu J, Gower MN, et al. Pharmacogenomic prescribing opportunities in percutaneous coronary intervention and bone marrow transplant patients. Pharmacogenomics. 2022 Feb;23(3):183-194.

Rodriguez Cairoli F, Appiani F, Sambade JM, et al. Efficacy and safety of opioid therapy guided by pharmacogenetics: a systematic review. Pharmacogenomics. 2021 Jun;22(9):573-586.

Rosenblat JD, Lee Y, McIntyre RS. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: a meta-analysis. J Affect Disord. 2018 Dec;241:484-491.

Rouby N, Alrwisan A, Langaee T, et al. Clinical utility of pharmacogene panel-based testing in patients undergoing percutaneous coronary intervention. Clin Transl Sci. 2020 May;13(3):473-481.

Saadullah Khani N, Hudson G, Mills G, et al. A systematic review of pharmacogenetic testing to guide antipsychotic treatment. Nat Ment Health. 2024;2(5):616-626.

Sági JC, Egyed B, Kelemen A, et al. Possible roles of genetic variations in chemotherapy related cardiotoxicity in pediatric acute lymphoblastic leukemia and osteosarcoma. BMC Cancer. 2018 Jul;18(1):704.

Scipher Medicine Corporation. PrismRA. 2023. Available at: https://www.prismra.com. Accessed June 4, 2026.

Singh JA, Saag KG, Bridges SL Jr, et al. American College of Rheumatology. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2016 Jan;68(1):1-25.

Skokou M, Karamperis K, Koufaki MI, et al.; Consortium of the PREPARE study in Greece. Clinical implementation of preemptive pharmacogenomics in psychiatry. EBioMedicine. 2024 Mar;101:105009.

Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023 Jan;82(1):3-18.

Stafford LK, Tang X, Brandt A, et al. Risk of anthracycline-induced cardiac dysfunction in adolescent and young adult (AYA) cancer survivors: role of genetic susceptibility loci. Pharmacogenomics J. 2024 Jun;24(4):21.

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Strand V, Cohen SB, Curtis JR, et al. Clinical utility of therapy selection informed by predicted nonresponse to tumor necrosis factor-α inhibitors: an analysis from the Study to Accelerate Information of Molecular Signatures (AIMS) in rheumatoid arthritis. Expert Rev Mol Diagn. 2022 Jan;22(1):101-109.

Swen JJ, van der Wouden CH, Manson LE, et al.; Ubiquitous Pharmacogenomics Consortium. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet. 2023 Feb;401(10374):347-356.

Tansey KE, Guipponi M, Hu X, et al. Contribution of common genetic variants to antidepressant response. Biol Psychiatry. 2013 Apr;73(7):679-682.

Tesfamicael KG, Zhao L, Fernández-Rodríguez R, et al. Efficacy and safety of pharmacogenomic-guided antidepressant prescribing in patients with depression: an umbrella review and updated meta-analysis. Front Psychiatry. 2024 Jul;15:1276410.

Tiwari AK, Zai CC, Altar CA, et al. Clinical utility of combinatorial pharmacogenomic testing in depression: a Canadian patient- and rater-blinded, randomized, controlled trial. Transl Psychiatry. 2022 Mar;12(1):101.

Vos CF, Ter Hark SE, Schellekens AFA, et al. Effectiveness of genotype-specific tricyclic antidepressant dosing in patients with major depressive disorder: a randomized clinical trial. JAMA Netw Open. 2023 May;6(5):e2312443.

Wang X, Wang C, Zhang Y, et al. Effect of pharmacogenomics testing guiding on clinical outcomes in major depressive disorder: a systematic review and meta-analysis of RCT. BMC Psychiatry. 2023 May;23(1):334.

Wong LYF, Sutcliffe AG, Ho CLT, et al. Clinical and cost-effectiveness of pharmacogenomic testing for anthracycline-induced cardiotoxicity in childhood cancer: a systematic review and meta-analysis. Front Pharmacol. 2025 Jul;16:1568320.

Xie F, Beukelman T, McCormick NP, et al. Use of a molecular signature response classifier to inform treatment selection improves clinical disease activity among patients with rheumatoid arthritis initiating a biologic or targeted synthetic disease-modifying antirheumatic drug. Arthritis Care Res (Hoboken). January 22, 2026. Online ahead of print.

Xu L, Li L, Wang Q, et al. Effect of pharmacogenomic testing on the clinical treatment of patients with depressive disorder: a randomized clinical trial. J Affect Disord. 2024 Aug;359:117-124.

Yang X, Li G, Guan M, et al. Potential gene association studies of chemotherapy-induced cardiotoxicity: a systematic review and meta-analysis. Front Cardiovasc Med. 2021 Jun;8:651269.

Zhang Y, Gao Y, Zou Y, et al. Comparative effectiveness of pharmacogenomic-guided versus unguided antidepressant treatment in major depressive disorder: new insights from subgroup and cumulative meta-analyses. BMJ Ment Health. 2025 Aug;28(1):e301726.

Zobdeh F, Eremenko II, Akan MA, et al. Pharmacogenetics and pain treatment with a focus on non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants: a systematic review. Pharmaceutics. 2022 Jun;14(6):1190.

Policy History/Revision Information

Date	Summary of Changes
10/01/2026	**Applicable Codes** • Updated list of applicable CPT codes to reflect quarterly edits; added 0697U **Supporting Information** • Archived previous policy version 2026T0587Y

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, 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).

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