Local Coverage Determination (LCD)

LCD - MolDX: Pharmacogenomics Testing (L38337)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
Noridian Healthcare Solutions, LLC	A and B MAC	02101 - MAC A	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02102 - MAC B	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02202 - MAC B	J - F	Idaho
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LCD Information

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Issue

Issue Description

This LCD outlines limited coverage for this service with specific details under **Coverage Indications, Limitations and/or Medical Necessity**.

CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A) allows coverage and payment for only those services that are considered to be reasonable and necessary.

42 CFR §410.32(a) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions

CMS Internet-Only Manual, Pub. 100-02, Medicare Policy Manual, Chapter 15, §80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests, §80.1.1 Certification Changes

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This is a limited coverage policy for pharmacogenomics testing (PGx) including single gene, multi-gene panels, and

combinatorial tests. These tests are generally covered (with a few exceptions) as described in further detail below to improve safety in the use of specific medications by avoiding potentially harmful medications, doses and/or adverse reactions known to occur with certain genotypes.

PGx testing is considered reasonable and necessary in limited circumstances as described below as an adjunctive personalized medical decision-making tool once a treating clinician has narrowed treatment possibilities to specific medications under consideration for use, or is already using a specified medication, based on other clinical considerations including the patient's diagnosis, the patient's other medical conditions, other medications, professional judgment, clinical science and basic science pertinent to the drug, and the patient's preferences and values.[1]

PGx tests must demonstrate analytical validity, clinical validity, and clinical utility to be considered reasonable and necessary for coverage. This is demonstrated through a required technical assessment of the test. PGx tests are considered germline tests and must adhere to other relevant germline testing policies published by this contractor.

It is understood that some panel/combinatorial tests may include content that has demonstrated clinical utility and some that has not. In such circumstances, this contractor may provide coverage for the components of tests that have demonstrated clinical utility when used in the proper clinical context described below.

Clinical Indications

PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B).

The selection of the medications in question must be derived from clinical factors/necessity rather than from a PGx test. Once the putative therapeutic agents are selected, and those agents are known to have gene-drug interactions as identified above, then a PGx test may be considered reasonable and necessary when the result of that test is necessary for the physician's decision-making process regarding safely administering or dosing the drug.

PGx testing is **not** considered reasonable and necessary merely on the basis of a patient having a particular diagnosis. Unless the record reflects that the treating clinician has already considered non-genetic factors to make a preliminary drug selection, PGx testing is not considered reasonable and necessary.

This LCD does not address (provides neither coverage nor non-coverage criteria) PGx testing for anticoagulation dosing, which is addressed by the National Coverage Determination (NCD) 90.1.

Definitions

For the purpose of this LCD, the following terms are defined as follows:

Gene – the term "gene" in this document will be used as a term to encapsulate all of the following: gene, pseudogene, and genetic locus.

Single-gene test - a laboratory test to detect relevant genetic variants (alleles) of 1 gene. If two or more different

single genes are ordered individually but simultaneously, this is not a panel but rather a couple of or multiple single gene tests.

Multi-gene panel – a laboratory test to detect genetic variants of at least 2 genes, wherein the clinician does not individually order genes, but orders a panel with a specified list of genes.

Combinatorial PGx test – a type of multi-gene panel that requires a proprietary algorithm to evaluate pharmacokinetic or pharmacodynamic relationships resulting in drug recommendations or warnings.

Actionable use – A test is considered to have an actionable use when the genotype information may lead to selection of or avoidance of a specific therapy or modification of dosage of a therapy. The selection, avoidance, or dose change must be based on the FDA-label for the drug, an FDA warning or safety concern, or a CPIC level A or B gene-drug interaction. An intended change in therapy based on the result of a genotyping test that is not supported by one of these sources is not considered an actionable use for the purposes of this LCD.

Coverage information

The clinical record must clearly show the use of or intent to prescribe a drug that has known drug-gene interactions that require a PGx test to be ordered to define the safe use of that drug in that patient.

If a treating clinician orders a single gene test or a test for a particular allele(s), but as a matter of operational practicality, the laboratory tests that single gene or allele on a platform that looks for variants in other genes/alleles as well, that particular test done in that particular instance is considered a single gene/allele test for coverage purposes. In this scenario the provider may bill for the component of the test that was reasonable and necessary (in this example, the single gene test).

A multi-gene panel is considered reasonable and necessary if more than one single gene on that panel would be considered reasonable and necessary for safe use of the medication in question or if multiple drugs are being considered (each fulfilling the criteria of actionable gene-drug interactions identified above) that have different relevant genes. Additionally, a gene panel must contain at a minimum all the necessary relevant gene/allele content required for their indicated use to meet clinical utility requirements. Such minimum criteria are determined by experts including relevant associations such as the Association for Molecular Pathology and are considered during the technical assessment. A multi-gene panel is not considered reasonable and necessary if only a single gene on the panel is considered reasonable and necessary.

If two or more single genes are tested, rather than a multi-gene panel, then the record must reflect that a clinician individually ordered each gene, and each single gene must individually be reasonable and necessary at the time they are ordered.

The ordering provider of a PGx test is restricted to providers who have the licensure, qualifications, and necessary experience/training to both diagnose the condition being treated and also to prescribe medications (the provider must be able to do both) for the condition either independently or in an arrangement as required by all the applicable state laws.

Test components that are not reasonable and necessary

Genes not identified as having actionable use are not considered reasonable and necessary. The algorithms employed in combinatorial testing are also not currently considered reasonable and necessary components of multi-

gene testing.

Technical requirements

The treating clinician receiving the laboratory report must be able to use the genetic information presented to guide treatment. To accomplish this, the laboratory must clearly report the clinical significance of the resultant genotype, based on empirical data or validated methodologies, as an annotation or interpretation. For clarity, the report should document the specific genotype-drug interaction that lead to the resultant interpretation.

A lab may test for a reference allele as a matter of exclusion (e.g. report that a patient has a reference allele when alternate alleles are not found). However, in such cases, the report must identify which allele is the reference allele and that the reference allele is reported as a matter of exclusion.

Noncovered Indications

PGx testing is not covered when a treating clinician is not considering treatment with a medication that has an actionable drug-gene interaction, or when the use of a medication with a drug-gene interaction is not reasonable and necessary.

Special Documentation Requirements

In order for any of the above services to be covered, the patient's medical record must clearly reflect the following:

1. The patient has a diagnosis for which pharmacologic therapy is reasonable and necessary, and the drug or drugs that the clinician is considering using must be reasonable and necessary for the treatment of the patient's diagnosis.
2. The clinician has made an initial personalized decision for the patient based on the patient's diagnosis, the patient's other medical conditions, other medications the patient is taking, professional judgement, clinical science and basic science pertinent to the drug (e.g., mechanism of action, side effects), the patient's past medical history, pertinent family history, and the patient's preferences and values.
3. The provider performing the service must have a record of what drug(s) is/are being considered and for what indication(s) to ensure the test performed is reasonable and necessary.

Summary of Evidence

Background

With improvements in genetic technologies and the recognition that inter-individual genetic differences may affect how patients metabolize or physiologically respond to pharmacologically active substances, PGx testing has been proposed as a way to personalize medication selection or dose based on a patient's individual genes.[2] The genes encoding the CYP2C19 and CYP2D6 proteins have emerged as having potential importance in the response (therapeutic or adverse) to numerous medications.[3-5] In addition combinatorial PGx tests have emerged, which find polymorphisms in a number of genes associated with pharmacologically important proteins.[6,7]

There is little question that such testing is now technically feasible, but for a test to be reasonable and necessary there must be sufficient evidence that it provides incremental information that changes physician management recommendations in a way that improves patient outcomes.

An abundance of research on genes and alleles (variants) has been published. To identify alleles and variants of importance, we reviewed FDA-approval documents, guidelines, and subject matter expert input.

PharmGKB is a commonly referenced resource of PGx information, particularly in following documented clinical validity and utility of relevant PGx biomarkers. PharmGKB curators create clinical annotations for gene-drug interactions and assign levels of evidence to the associations based on published evidence.[8] As an example, the database contains annotations regarding 102 drugs from 3 guidelines[9] for drugs relevant to psychiatry, an area where PGx testing is done routinely. CPIC is a common source of guidelines. This group has been described by Dr. Annette Taylor[10]:

CPIC is an NIH-funded organization with a membership of more than 300 clinicians, scientists, laboratorians, and others knowledgeable about pharmacogenetics with the purpose of facilitating the use of pharmacogenetic test results for patient care. CPIC's goal is to address this (potential) barrier by creating freely available, peer-reviewed, evidence-based, and updatable gene/drug clinical practice guidelines. A CPIC Overview Presentation can be found at https://cpicpgx.org/resources/.

CPIC uses a rigorous and systematic system to grade levels of evidence, and only gene/drug groupings with strong evidence for actionable prescribing are selected for guideline development.

CPIC guidelines help clinicians understand how to use available genetic test results to guide prescribing.

At present, CPIC has 23 guidelines for the dosing and administration of 46 drugs based on gene-drug interactions.[11] As part of this process, CPIC reviews the clinical evidence for gene-drug interactions and assigns clinical utility "levels" reflecting their confidence in the evidentiary basis for clinicians to alter their drug administration or dosage. The CPIC levels are A, B, C, and D. The process for this determination and the definition of each category are demonstrated in the figure (attached to this LCD) and table below.[12]

CPIC Level	**Clinical Context**	**Level of Evidence**	**Strength of Reco**
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moder (change in prescrib
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing	Preponderance of evidence is weak with little conflicting data	At least one option prescribing) is reco
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or	Evidence levels can vary	No prescribing acti

	otherwise impractical or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests		
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed	Evidence levels can vary	No prescribing acti

The following are examples of genes that are commonly tested for gene-drug interactions, and evidentiary review by CPIC have resulted in a level A or B rating:

CYP2C9

The CYP2C9 protein has clinical significance in the metabolism of several drugs including phenytoin (CPIC Level A).[11,13] The recently FDA-approved drug Mayzent, which is indicated for the treatment of multiple sclerosis requires CYP2C9 genotyping for dosing in accordance with the FDA prescribing information.[14] Since this LCD does not address PGx for warfarin dosing, alleles and variants relevant to warfarin are not reviewed here. The following alleles are both common and are believed to have clinical significance for phenytoin dosing: *2, *3, *5, and *6, and a joint recommendation from the Association for Molecular Pathology and the College of American Pathologists has recommended that these variants be included as part of a CYP2C9 test.[15] The *1, *2, and *3 alleles are necessary to safely dose the newly FDA-approved drug Mayzent.[14]

CYP2D6

CYP2D6 is a clinically important enzyme in the metabolism of a large number of medications and has CPIC level A or B gene-drug interaction and dosing guideline.[11] A number of particular alleles have been reviewed as having actionable use including: *3, *4, *5, *6, *7, *10, *17, and *41, *1xN, and *2xN. Drugs that may require *CYP2D6* testing for safe administration include iloperidone, clozapine, duloxetine, deutetrabenazine and valbenazine, among others.

CYP2C19

CYP2C19 is a clinically important enzyme in the metabolism of a number of selective serotonin reuptake inhibitors as well as tricyclic antidepressants with a CPIC level A or B gene-drug interaction and dosing guideline[11,13]. Recently published recommendations, including a report of the Association of Molecular pathology, recommend the following alleles be included in testing as a minimum based on clinical importance and population frequency: *2, *3, *17.[13,16]

HLA testing

Several specific *HLA* alleles are recommended for testing including some relevant psychiatric medications.[13] They include *HLA-B*15:02* and *HLA-A*31:01*. Both of these have level A or B gene-drug recommendations from CPIC and

are relevant to the use of carbamazepine and oxcarbazepine. Other relevant variants in these genes include *HLA-B 57:01* and *HLA-B 58:01*, which are relevant to the use of abacavir and allopurinol.

For more information, the FDA has subsequently published a listing of gene-drug interactions found in drug labels that should be considered when using those medications.[17]

Subject Matter Panel and Contractor Advisory Committee (CAC) Meeting on June 26th, 2019

In order to get a better understanding of expert opinion of PGx testing and CPIC guidelines, a panel of subject matter experts and Carrier Advisory Committee (CAC) members from CGS, Wisconsin Physicians Services, Noridian, and Palmetto GBA was convened on June 26th, 2019, via teleconference. While only invited experts and CAC members could speak, interested members of the public who registered could listen. The full recording is also available.[18] Subject matter experts on the panel included the list below. Included members may have additional titles and positions to those listed.

Mary Relling, Chair, Pharmaceutical Dept. St. Jude Children's Research Hospital

John Greden, Founder and Executive Director, University of Michigan Comprehensive Depression Center

Annette Taylor, AVP, LabCorp, Co-Business Lead, Pharmacogenomics

Stuart Scott, Associate, Associate Professor, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai

The panel generally agreed that PGx testing has the ability to provide clinically utile information that allows treating clinicians to select and dose particular medications appropriately. PGx testing (presumably for genes associated with pharmacokinetic pathways) was described as being analogous to measuring renal function with a serum creatinine prior to dosing renally cleared medications. The panel generally agreed that single gene testing and multi- gene panels (as defined at the top of this LCD) have a role in medication dosing and selection. The panel members did not specifically recommend or support the use of any combinatorial PGx test or differentiate one over another. There was general agreement that combinatorial PGx tests with a proprietary algorithm not available for public review required independent evidence establishing their validity and utility. Additionally, a comment was made that *CYP2C19* and *CYP2D6* testing would most likely be the appropriate comparator in a clinical study to determine if a combinatorial PGx test provides information that improves outcomes more than single gene or multi-gene panels.

A CAC member commented that PGx testing is becoming increasingly common, and it should not be restricted by provider type.

Additional Expert Input from the CAC

In addition to the panel, a number of experts who were unable to attend provided written correspondence. These included the following:

John Logan Black, Co-Director, Personalized Genomics Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic

To summarize, Dr. Black’s comment generally agreed with the comments of the panel. He indicated support for the

use of genetics in guiding pharmacologic treatment, and in referencing guidelines from CPIC and the FDA. He also provided references to a number of peer-reviewed studies which have been reviewed in this LCD. As regards combinatorial testing, he noted that evidence does support their use, though he also noted that it "is unclear whether the power of combinatorial PGx is driven by a few genes or if it is absolutely due to the combinatorial effects." While it was not discussed by the panel, a manuscript (describing the GUIDED study) submitted by Dr. Black did a retrospective comparison (using statistical modelling rather than a direct comparison) of GeneSight to single gene testing.[19] This study suggested that combinatorial testing predicts poor antidepressant response and outcomes better than single gene testing. Two gene panels were not considered.

He indicated that for panel testing, he would recommend a minimum panel in psychiatry consisting of the genotypes of *CYP2C9, CYP2C19, CYP2D6, HLA-A*31:01* and *HLA-B*15:02*.

Jose DeLeon, Professor, Psychiatry, University of Kentucky

Dr. de Leon's comments largely agree with the panel's comments as well, though he specifically noted the clinical utility of HLA-B*15:02 in any patient of Asian ancestry before starting carbamazepine, and for *CYP2D6* and *CYP2C19* for some antidepressants and some antipsychotics. Additionally, Dr. de Leon also indicated his belief that the evidence did not support the use of GeneSight. Notably, he indicated the importance of *CYP2D6* and *CYP2C19* and questioned the testing of other CYP genes. He also noted that the GUIDED study (reviewed above) "further demonstrated that the study results were negative, and the authors had to use secondary outcomes to try to demonstrate that a negative study had positive results."

Bruce Cohen - Director of the Program for Neuropsychiatric Research at McLean Hospital and Harvard Medical School

Dr. Cohen voiced concern for the use of PGx testing in drug selection. He noted that the FDA has published a document raising concerns about PGx testing for general use in psychiatry.[20] The document notes: "…the relationship between DNA variations and the effectiveness of antidepressant medication has never been established.'' It goes on to state as a recommendation to providers:

If you are using, or considering using, a genetic test to predict a patient's response to specific medications, be aware that for most medications, the relationship between DNA variations and the medication's effects has not been established.

However, the document also notes:

There are a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared or approved genetic tests and FDA approved medications. The FDA authorized labels for these medical products may provide general information on how DNA variations may impact the levels of a medication in a person's body, or they may describe how genetic information can be used in determining therapeutic treatment, depending on the available evidence.[18]

A manuscript examining the metascience of PGx testing and providing an accompanying viewpoint reviewed 10 clinical studies of PGx in psychiatry and found that none of them were blinded and used a protocol-based comparison.[21] The authors point to two evidence-based protocols that are freely available and could have been used, STAR*D and the Texas Medication Algorithm Project. As the authors state early on:

Simply put, MDD [Major Depressive Disorder] is determined by a large number of genes, and, except in rare cases,

no single gene or limited gene set, even those for drug metabolism and drug targets, determines more than a few percent of the risk of illness or course of treatment.

The STAR*D study included 2,876 subjects with major depressive disorder from multiple institutions.[23-24] In this study all participants started with citalopram as the initial treatment and may have advanced through additional levels of treatment up to level 4. If a subject did not respond at a given level, that subject was then advanced to the next level of treatment, which included alternative treatments instead of or in addition to the treatment the patient was on.

Cohen suggests that PGx tests offer no clear clinical value over freely available and well-established protocols for drug selection with a reference to a number of recent documents.[20,21] He also suggests that, should a clinician be unsure about drug choice, a psychiatry consultation costs substantially less money than PGx testing.

Additional comments of support

This contractor received numerous comments on this proposed policy. Of note, we received letters of support for coverage of PGx testing as described in this policy by prominent associations including the Association for Molecular Pathology, the College of American Pathologists, and the American Psychiatric Association.

Evidence for the utility of combinatorial PGx testing

A review of the available evidence found five combinatorial PGx tests for which outcome data has been published. These studies focus on testing for drug selection for psychiatric and neurological use, and include tests such as CNSDonse, Genecept, Neuropharmagen, Genesight, and NeuroIDGenetix.

A review of the published clinical studies performed demonstrated that, despite showing some promising findings, these studies had several shortcomings in that they failed to meet their primary endpoints,[25-28] were not representative of the Medicare population,[29-32] or had other significant shortcomings such as a possible biased sample population.[26,29-31,33]

Some of these studies yielded interesting observations, for example, Tanner et al[34] that demonstrated that greater improvement in treatment success was seen by primary care providers using a combinatorial PGx test than compared to psychiatrists who did not see a significant benefit, although there was no difference identified between the psychiatrist-treated and primary care treated groups. Many of these studies saw differences in performance from using these genetic tests vs. standard of care with the limitations noted above.

We found two meta-analyses of combinatorial PGx with overlap in the studies reviewed, the statistical techniques, and the results. Both meta-analyses included studies that are cited above. All the tests studied in these meta-analyses included *CYP2D6* and *CYP2C19*. Both pooled data using a random effects model. The meta-analysis published by Rosenblatt, Lee, and McIntyre,[35] pooled the results of 6 studies and found a pooled relative risk for treatment remission of 1.71 in favor of PGx testing, and a relative risk of 1.36 for remission, also favoring testing. A more recent meta-analysis by Bousman et al[36] included 5 studies and found a pooled relative risk for treatment remission of 1.74 in favor of PGx testing. A pooled relative risk for response was not reported. Both of these meta-analyses found a high level of heterogeneity, and the paper by Rosenblatt, Lee, and McIntyre suggested that this makes it difficult to assume that there is a class effect. Additionally, because combinatorial PGx tests rely on many of the same PGx biomarkers tested in single and multi-gene PGx tests, it has been postulated based on an observational study utilizing GeneSight that there may be little gained from the proprietary algorithms in these tests above single and multi-gene panels.[37] It should be restated here that our CAC experts were consistent in their lack

of support for the use of combinatorial PGx and cited similar questions; additional comments received from societies such as the Association for Molecular Pathology, the College of American Pathologists, and the American Psychiatric Association similarly stated that the validity and utility of combinatorial testing has not been demonstrated. Of note, a more recent review submitted by the APA concludes that "there is insufficient evidence to support widespread use of combinatorial pharmacogenetic decision support tools at this point in time" and noted that "a high level of evidence has been achieved only for the cytochrome P450 genotype data".[38]

Analysis of Evidence (Rationale for Determination)

We implemented numerous levels of evidence in the hierarchical framework of Fryback and Thornbury[39] and utilized the ACCE Model Process for Evaluating Genetic Tests in this policy.[40]

When a physician is treating a patient for a particular diagnosis, there are often many available treatment options. The physician may go through a series of decisions and use numerous sources of information, including evidence, professional judgement, and patient values and preferences to narrow down the treatment approach from an array of potential treatments to the selection of a specific treatment or course of treatment. The optimal medication for a particular patient is a decision to be made by the physician and patient. The evidence reviewed by this contractor clearly suggests that PGx testing has the ability to predict how a patient will metabolize a number of specific drugs, and some evidence suggests that this can be used as a tool for safe drug administration. The putative clinical utility of PGx testing comes from the ability to link genotype to phenotype and then to link phenotype to medication selection (which may include avoidance) or medication dosing. There appears to be general agreement within the scientific community that for some alleles of some genes there is a clear phenotype, and that the phenotype has an established interaction with particular drugs. There also appears to be supporting evidence (including guidelines) that specific medication selection decisions (including dosing and avoidance) may be made based on genotypes and phenotypes. The CPIC level categorization process, as reviewed, follows a similar evidentiary process for evaluating clinical utility as used by this contractor, and similar to other expert organizations, carries weight in its findings with surveyed experts in the field. When employed in the proper clinical context, following FDA labels and/or CPIC Level A and B grading are likely to improve clinical outcomes by avoiding unsafe medications or doses based on genotype-drug interactions that are clearly described.

Since the medical necessity for testing a gene in PGx can only come from the ability of that test to inform a management decision based on a gene-drug interaction, a test for a specific gene or allele is not reasonable and necessary unless and until a clinician is considering using a drug that has an interaction with a specific gene or allele. Once this initial decision has been made it may be reasonable and necessary to test for that allele or that gene. If a clinician is not considering using a medication with an interaction with a gene being tested, or if the patient who is being tested is unable or unwilling to use a medication interacting with the gene or allele being tested, then there is no benefit to the patient to run a test of that gene or allele.

It should be pointed out, however, that there are several remaining uncertainties in the evidence.

While there are some large PGx studies, we are not aware of large high-quality studies that used a clear evidence-based prescribing approach in the control arm. As a number of prominent psychiatrists with expertise in the biological underpinnings of mental health have pointed out, it is not clear that PGx testing is a better tool for drug selection than using a standardized evidence-based protocol which does not rely on genetics, or a consultation from a knowledgeable provider. Moreover, psychiatric conditions wherein a lot of PGx testing is performed have significant

complexity involving many genes and factors outside of PGx. As such, while the evidence does suggest that PGx testing can be used to refine the selection of a medication or dose, there is not sufficient evidence to suggest that PGx testing is reasonable and necessary for the initial selection of potential medications to treat a patient.

Combinatorial PGx testing

Because these tests leverage many of the same biomarkers already discussed above and because these tests are defined by the proprietary algorithms required to associate pharmacokinetic and pharmacodynamic events, this contractor has determined that the evidentiary review of clinical validity and utility of these tests should be demonstrated beyond the capability of single gene and multi-gene panel information already evaluated and established. The algorithms themselves (or more than the sum of the FDA and CPIC Level A and B biomarker information) must establish validity and utility to have independent value to establish coverage. Based on our review of the evidence and on expert feedback submitted both during the CAC meeting and during the comment period for this policy, it's been determined that there are insufficient data to support coverage for any combinatorial test. This conclusion was also reached by the CAC committee members and professional societies whom all agreed that the combinatorial component of panel tests have not to date demonstrated independent value. However, it should also be noted that combinatorial tests are a subtype of multi-gene PGx tests, and there may be components within those tests that are necessary and reasonable and thus may be covered.

This policy does not restrict use of PGx testing to provider type. While it is possible that specialists in mental health or PGx are more likely to be aware of a potential gene-drug interaction in medications used to treat mental illness, the data reviewed above support the conclusion that the actionability of the resultant information is not dependent on who submits the order. This conclusion is in keeping with the CAC discussion held on June 26th, 2019, which, together with written comments submitted during the comment period, communicated a high degree of agreement among discussants and commenters that there is not a reason to limit the coverage by provider type.

In summary, the present evidence does not clearly demonstrate that routine PGx testing for the purpose of medication selection offers a benefit over selection of medications based on contemporary evidence-based medication selection protocols. However, there are clear biological pathways driven by specific genes which may affect concentrations of a drug that a patient experiences, including drugs that are components of evidence-based protocols. As such, when a clinician is specifically considering using a drug, because a clear evidence-base or individualized factors make it one of the most appropriate potential treatments, and that medication has a clinically important drug-gene interaction, the evidence suggests that testing the gene can help refine that initial medication selection by avoiding an unsafe or ineffective medication or by leading to a change of dose.

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
07/03/2025	R2	Under **Bibliography** revised the broken hyperlink for the 40th reference and changes were made to citations to reflect AMA citation guidelines. Updated **Analysis of Evidence (Rationale for Determination) paragraphs** #1, #5, and #8 to mirror the paragraphs used presently by the MolDX team at Palmetto GBA as part of an annual review. Revision history dates and language may not exactly match the MolDX PGBA revision history. However, these revisions do not change coverage or guidance.	• Provider Education/Guidance
08/24/2023	R1	Under **CMS National Coverage Policy** added the following regulations, "Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), 42 CFR §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions, and CMS Internet-Only Manual, Pub. 100-02, Medicare Benefit Policy Manual, Chapter 15, §80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests, §80.1.1 Certification Changes". Under **Bibliography** changes were made to citations to reflect AMA citation guidelines. Formatting, punctuation and typographical errors were corrected throughout the LCD.	• Provider Education/Guidance

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

A57385 - Billing and Coding: MolDX: Pharmacogenomics Testing

A58238 - Response to Comments: MolDX: Pharmacogenomics Testing

LCDs

DL38337 - MolDX: Pharmacogenomics Testing (MCD Archive Site)

Related National Coverage Documents

NCDs

90.1 - Pharmacogenomic Testing for Warfarin Response

Public Versions

UPDATED ON	EFFECTIVE DATES	STATUS
06/26/2025	07/03/2025 - N/A	Currently in Effect (This Version)
08/18/2023	08/24/2023 - 07/02/2025	Superseded
Some older versions have been archived. Please visit the MCD Archive Site to retrieve them.		

Keywords

N/A