

Proposed Local Coverage Determination (LCD): MolDX: Combinatorial Pharmacogenomics Limited Coverage (DL35633)

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Proposed LCD

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Palmetto GBA	A and B MAC	10111 - MAC A	J - J	Alabama
Palmetto GBA	A and B MAC	10112 - MAC B	J - J	Alabama
Palmetto GBA	A and B MAC	10211 - MAC A	J - J	Georgia
Palmetto GBA	A and B MAC	10212 - MAC B	J - J	Georgia
Palmetto GBA	A and B MAC	10311 - MAC A	J - J	Tennessee
Palmetto GBA	A and B MAC	10312 - MAC B	J - J	Tennessee
Palmetto GBA	A and B and HHH MAC	11201 - MAC A	J - M	South Carolina
Palmetto GBA	A and B and HHH MAC	11202 - MAC B	J - M	South Carolina
Palmetto GBA	A and B and HHH MAC	11301 - MAC A	J - M	Virginia
Palmetto GBA	A and B and HHH MAC	11302 - MAC B	J - M	Virginia
Palmetto GBA	A and B and HHH MAC	11401 - MAC A	J - M	West Virginia
Palmetto GBA	A and B and HHH MAC	11402 - MAC B	J - M	West Virginia
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MolDX: Combinatorial Pharmacogenomics Limited
Coverage

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Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to

improve the functioning of a malformed body member.

Title XVIII of the Social Security Act, §1833(e), prohibits Medicare payment for any claim lacking the necessary documentation to process the claim.

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This is a limited coverage policy for GeneSight®, NeuroIDGenetix, and other combinatorial pharmacogenomics panels in the treatment of psychiatric illness when ordered by a psychiatrist. GeneSight® and NeuroIDGenetix are covered for patients in whom a two gene panel consisting of CYP2C19 and CYP2D6 is reasonable and necessary. The policy MolDX: Pharmacogenomics Testing DL38294 contains complete information. All requirements contained in MolDX: Pharmacogenomics Testing DL38294 must be met.

In summary, combinatorial pharmacogenomics testing (please see definition below) is considered reasonable and necessary in limited circumstances as described in this Local Coverage Determination (LCD) as an adjunctive personalized medicine decision-making tool once a treating clinician has narrowed treatment possibilities to a small group of specific medications based on other 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.

Combinatorial pharmacogenomics testing is not considered reasonable and necessary merely on the basis of a patient having a particular diagnosis. Additionally, if the record does reflect that the treating clinician has already considered non-genetic factors to make a preliminary prescribing decision, pharmacogenomics testing is not considered reasonable and necessary. Rather such testing may be considered reasonable and necessary if a particular treatment is being considered for the patient’s diagnosis, and there is a significant gene-drug interaction of concern.

A combinatorial pharmacogenomics test is multi-gene panel that examines polymorphisms in several or more genes that interact themselves or encode proteins that interact in a pharmacokinetic or pharmacodynamic manner with medications. These tests may also include some type of an algorithm to generate recommendations or warnings based on the results of the polymorphisms identified among the genes tested. Such tests have typically been developed with the intent of allowing physicians to select, avoid, or appropriately dose medications so as to achieve an optimal response without the need for trial and error or to avoid adverse drug events.

~~Based on current Clinical Pharmacogenetic Implementation Consortium (CPIC) gene-drug interaction levels,~~ GeneSight® and NeuroIDGenetix are covered when a provider is already considering (i.e. considering prior to the order for the test being placed) at least one drug from list A and at least one drug from list B. However, as new level A and B interactions are identified additional drugs may be considered indications for testing.

List A	List B
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amitriptyline	amitriptyline
citalopram	atomoxetine
clopidogrel	codeine
escitalopram	fluvoxamine
clomipramine	nortriptyline
doxepin	ondansetron
imipramine	oxycodone
sertraline	paroxetine
trimipramine	tramadol
	aripiprazole
	brexpiprazole
	clomipramine
	desipramine
	dextromethorphan
	doxepin
	imipramine
	methylphenidate
	mirtazapine
	pimozide
	protriptyline
	quinidine
	risperidone
	sertraline
	trimipramine
	venlafaxine
	vortioxetine

Summary of Evidence

Background

With improvements in genetic sequencing technology and the recognition that inter-individual genetic differences may affect how patients metabolize or physiologically respond to pharmacologically active substances, pharmacogenomic testing has been proposed as a way to personalize medication selection or dose based on a patient's individual genes.¹ The genes encoding the CYP2C19 and CYP2D6 genes emerged as genes of potential importance in the response (therapeutic or adverse) to numerous medications²⁻⁴. In addition, combinatorial pharmacogenomics panels have emerged, which find polymorphisms in a number of genes associated with pharmacologically important proteins.^{5,6}

With the advance of sequencing technology, 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.

While pharmacogenomics testing has the potential to change medication management in many health conditions, there appears to be little if any evidence assessing the clinical outcomes of combinatorial pharmacogenomic tests outside of neuropsychopharmacology, as such the rest of this evidence review is limited to this group of tests.

Pharmacogenomic Testing in Psychiatric Disease

Clinical Need and Bioplausibility

In 2017, 17.3 million adults (7.1%) had at least one major depressive episode (MDE) in the past year, with 11.0 million of those adults having an MDE with severe impairment in the past year.⁷

Depression is common among older adults, and is associated with disability as well as significantly decreased quality of life, and evidence regarding the treatment of depression in later life is still not well developed.⁸ Treatment using antidepressant medications is a well-accepted treatment approach, though existing research suggests that many patients may not respond to treatment,^{9,10} and a review of clinical practice guidelines for the treatment of depression following failed initial treatment noted a common theme of trial of an alternative agent, though there was little consistency regarding how to select such an agent or dose it.¹¹

Evidence has emerged that variants in CYP genes and Serotonin genes may partially explain how well a patient responds to and/or tolerates psychiatric pharmacotherapy, with the most evidence for polymorphisms in CYP2D6 and CYP2C19, suggesting that use of genetic information may be able to guide treatment.³

Combinatorial Pharmacogenomics Tests

A review of the evidence found five combinatorial pharmacogenomics tests for which outcome data has been published.

CNSDose

CNSDose is a test that looks for polymorphisms in the genes for the CYP450 system and the blood brain barrier. We were able to find one published outcomes study for the test.¹² The study enrolled 152 subjects, who were each randomized to genetically unguided treatment (control group) or genetically guided treatment, with 148 patients completing the study. Patients were considered eligible for inclusion if that had a diagnosis of Major Depressive Disorder (MDD), and no other active psychiatric diagnoses. Patients were excluded if they were co-prescribed known CYP2C19, CYP2D6, or ABCB1 inducers or inhibitors. Patients with hepatic and renal impairment were also excluded. The eligible ages for inclusion were not clear, but the average age of subject in the control group was 44.3 years,

and the average age in the genetically guided group was 44.2 years. The average proportion employed in the control and genetically guided groups were 89% and 91% respectively.

The remission rate was 72% in the genetically guided group and 28% in the control group ($p < 0.0001$). Medication intolerability was also higher in the control group ($p = 0.0272$).

Given that the average age was less 45 years old, with average employment of around 90%, and patients who had hepatic or renal impairment were excluded, the population studied seems to have little if any overlap with the population whom Medicare statutorily represents. We were unable to find additional research in a population more representative of the Medicare population.

Genecept

The Genecept Assay is a test looking for polymorphisms in CYP2D6, CYP2C19, CYP3A4, SLC6A4, 5HT2C, DRD2, CACNA1C, ANK3, COMT, and MTHFR. We were able to find one published study with outcomes¹³, which was a single arm observational study. The study was described as a “naturalistic” study looking at outcomes in a single arm of 675 unique patients whose physicians had ordered this test. The average patient age was 40.5 years. The majority was employed full time or part time or was a student, and 24% were not currently employed, possibly due to disability.

Data was collected from physician assessment and patient self-assessment. The majority of patients had a mood disorder, though patients with attention-deficit hyperactivity disorder, schizophrenia, schizoaffective disorder, cognitive disorder substance-related disorder, developmental disorders, and personality disorder were also included. Descriptive statistics are reported, including that for depression 38% of patients achieved remission, and 39% achieved response.

The authors of the study include in their conclusion the following limitation: “...it is challenging to estimate the specific effectiveness of genetic testing as distinct from placebo-like effect.” Later on they state: “Future studies are needed to estimate the magnitude of clinical utility of genetic testing in the general psychiatric population as compared to treatment as usual.”

Additionally, the sample studied does not appear to be representative of the Medicare population.

Neuropharmagen

Neuropharmagen is a pharmacogenomics test that combines genetic data along with drug interaction information and disease information into an algorithm to create a report giving drugs a green, yellow, or red box. Drugs associated with a green box are likely to give a positive response. Drugs with a yellow box are recommended to be given with caution and increased monitoring. A red box suggests a higher risk of adverse events. Polymorphisms associated with the following particular genes are examined: ABCB1, AKT1, BDNF, CACNG2, CES1, COMT, CRHR1, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, DDIT4, DRD3, EPHX1, FCHSD1, GRIK2, GRIK4, HLA-A, HTR1A, HTR2A, HTR2C, LPHN3, NEFM, OPRM1, RGS4, RPTOR, SLC6A4, UGT2B15.¹⁴ (see supplement 1)

Neuropharmagen has two published outcomes studies^{14,15}

The study by Perez¹⁴ was a randomized trial in which 316 patients from Spain with a principal diagnosis of major depressive disorder who were at least 18 years of age were randomized to receive either test-guided treatment (study group) or a control group receiving treatment as usual without the guidance of the test. Secondary

comorbidity psychiatric diagnoses were not grounds for exclusion from the study. Patients requiring treatment with at least one of three specific known strong CYP2D6 inhibitors were excluded: quinidine, cinacalcet, and terbinafine. The average age in the study group was 51.74 years, and the average age in the control group was 50.74 years. The average number of previously failed medication trials was 2.55 in the study group and 2.57 in the control group.

The primary outcome was given by the study investigators as a sustained response (defined as response to treat at two consecutive interviews) through the 12 week follow-up period. A difference in this primary outcome was not observed with a 38.5% response in the study group and a 34.4% response in the control arm ($p = 0.474$).

The study by Han¹⁵ randomized 100 Korean patients to either treatment informed by pharmacogenomics testing or a control arm. Patients were included if they were 20 years old or older and had major depressive disorder. Patients were excluded if they had significant comorbid psychiatric disease. The primary outcome measure was change in 17-item Hamilton Depression Rating Scale from baseline to 8 weeks. The average age of subjects studied was 44.2 years in the guided treatment arm and 43.9 years in the control arm of the study. The employment statistics revealed that 21.2% of those in the pharmacogenomically guided treatment arm were employed compared with 29.2% in the control arm.

The study found that the guided arm had a HAMD reduction of 16.1, and the control arm had a HAMD reduction of 12.1, favoring the use of pharmacogenomically-guided treatment ($p = 0.010$).

Both of these studies include a population that is younger than the typical Medicare population. Additionally, with a disease that has significant social and cultural ramifications, it is difficult to understand how well the populations studied and the results in the populations studied could be extrapolated to the population of Medicare beneficiaries in the United States.

GeneSight®

GeneSight® is a test that uses genotype data from 6 different genes: CYP2D6, CYP2C19, CYP2C9, CYP1A2, SLC6A4, and HTR2A to determine a patient's composite phenotype. Based on this, drugs are binned into green, yellow, and red bins, corresponding to "Use as directed," "Use with caution," and "Use with increased caution and more frequent monitoring" respectively. The report also identifies common drug-drug interactions that are similarly influenced by the patient's genetic composition.

A number of studies examining the impact of GeneSight's use on patient outcomes have been published:

Hall-Flavin 2012

A prospective observational pilot study of two cohorts, those treated using GeneSight® ($n = 22$) vs. those treated without pharmacogenomics guidance ($n = 22$), was undertaken¹⁶. Patients with a primary diagnosis of MDD or depression not otherwise specified with a minimum score of 14 on HAM-D17 were enrolled. Samples were collected at baseline in both arms, while only the physicians in the GeneSight® arm were provided with test results to inform treatment decisions. In addition to the prospective comparisons, retrospective analysis in the TAU subjects at the end of the study was implemented after un-blinding the GeneSight® results to test for clinical validity.

The primary outcome measure was change in the HAMD score at 8 weeks. A greater reduction in depression scores from baseline to the week 8 visit was observed in the HAMD ($p = 0.04$). In all measures, a faster reduction of symptoms was observed in the GeneSight® arm subjects compared to the TAU arm subjects.

Physicians changed medications more often for subjects in the GeneSight®-guided group (57.9%) than the unguided group (25.9%) ($p = 0.0007$). Of the 15 GeneSight®-guided subjects classified in the red bin category at baseline, fourteen (93.3%) experienced a medication change or dose adjustment during the eight week study period, compared with 8 out of 18 subjects in the unguided group (44.4%) in the red bin category ($p = 0.002$). A significant association between bin status and outcome was observed within the unguided group ($p = 0.028$). Subjects classified in the red bin category had less improvement (11%) than those classified in the green or yellow categories (31.9%, $p = 0.047$), further demonstrating the deleterious effects of red bin medications on patient outcomes.

Hall-Flavin 2013

Following the Hall-Flavin (2012) study, a replication study by the same authors was performed.¹⁷ This was a prospective study of two successive cohorts of patients. This study enrolled 230 patients in a study assessing genetically guided vs. unguided treatment. Enrollment into each cohort was successive rather than randomized, with enrollment in the guided group immediately following the unguided group. In the unguided group genotyping was performed, but the report was not shared with the physician. In the guided group the report was shared.

The average age was 44.0 years in the unguided group and 41.0 years in the guided group. The mean number of baseline medications tried in the unguided group was 4.7 as compared with 3.6 medications in the guided group ($p = 0.021$). Phenotype distribution for 5 genes were reported in each group, and there was a statistically significant difference ($p = 0.03$) between the CYP2D6 phenotypes in the guided vs. unguided group with the unguided group having more extensive and ultrarapid metabolizers, and the unguided group having more intermediate and poor metabolizers.

A single primary outcome measure was not given, but differences in score pre-treatment to 8 weeks of treatment were reported for a number of measures including the HAMD, Quick Inventory of Depressive Symptomatology – Clinician Rated 16 Item, and Patient health Questionnaire – 9 item. Results were statistically significantly different for all of them,

Winner 2013a

An observational study in collaboration with Union Health Services (a staff model HMO located in Chicago, Illinois), examined healthcare utilization in relation to medication categories (binning) using GeneSight®.¹⁸ Ninety-six patients previously diagnosed with a depressive disorder or anxiety disorder and treated with one of the medications included in the GeneSight® panel were included in the study. The GeneSight® bin assignments of patient psychiatric medications were compared to the medical records for patient medication prescriptions, healthcare utilization, medical absence days, and disability claims for the previous 12 months. It was found that subjects whose medication regimen included a medication in the red bin had 69% more total healthcare visits ($p = 0.005$), 67% more general medical visits ($p = 0.02$), greater than 3-fold more medical absence days ($p = 0.06$), and greater than 4-fold more disability claims ($p = 0.004$) than subjects taking drugs in the green.

Winner 2013b

The above studies were observational studies. Following these a small randomized controlled trial was undertaken, in which 51 patients were randomized to receive genetically guided treatment or usual care.¹⁹ Patients with a diagnosis of depression were included. Patients were excluded if they had bipolar disorder, schizophrenia, schizoaffective disorder, or active substance abuse or dependence. The mean age was 47.8 years in the usual care arm and 50.6 years in the genetically guided group.

All subjects were genetically tested using the assay. In the usual care arm, the provider treated the patient without knowledge of the test results, while in the genetically guided group; the provider was given the test results to allow for Medication selection. The percent improvement in HAMD score from baseline to 10 week follow-up was 20.7% for the usual care group and 30.8% for the GeneSight® group ($p=0.29$). Data on CYP phenotype distribution was not provided.

GUIDED Trial

All of the above studies were either not randomized or were small. To improve the evidence quality, the Genomics Used to Improve Depression Decisions (GUIDED) trial was undertaken.²⁰ This was a large randomized trial in which 1,514 patients were enrolled in the study. Inclusion in the study required that a patient be over 18 years of age and have major depression with inadequate response to at least one psychotropic medication. Patients were treated for depression by their prescribing providers. All subjects enrolled had baseline pharmacogenomics testing, but only those in the guided treatment arm had the results known to their prescribing providers. For those enrolled in the treatment as usual arm, the providers prescribed medication without any pharmacogenomic information. The ages of enrolled subjects ranged from 18 to 90 years, with 13.2% of the patients who completed the baseline visit being over age 65 years.

The study lasted for 24 weeks, but the primary outcome measure was continuous change in HAMD score at week 8. There was no statistically significant difference in this outcome measure ($p=0.107$). There were statistically significant differences in response ($p=0.01$) and remission ($p=0.007$) between the two groups.

Tanner et al

In addition to the above studies, one study attempted to evaluate outcomes from the use of GeneSight® by psychiatrists to guide treatment as compared with the use of GeneSight® by primary care providers.²¹ This was a 7 year unblinded observational study comparing the effects of GeneSight® guided treatment among primary care providers versus among psychiatrists. A total of 1871 patients were included in the analysis with a median age of 41.2 years, 94.3% of whom were under 65. The cohort treated by psychiatrists was similar to the cohort treated by primary care providers in the gender distribution and mean age. However, there were statistically significant differences in the fraction of patients with a psychiatric condition other than depression, the presence of a comorbid psychiatric condition, number of psychiatric medications at baseline, and baseline Beck Depression Inventory (BDI) score. In general, the authors found greater treatment success in the patients treated by a primary care provider as compared with those treated by a psychiatrist. Patients treated by a primary care provider were statistically significantly more likely to achieve a decrease in the BDI score, response, and remission than those treated by a psychiatrist.

Macaluso 2018

An observational study attempted to elucidate the distribution of medication bins assigned by GeneSight®.²² The authors reviewed the 22 antidepressant recommendations from the last 19 patients who had received the test to get a distribution of the frequency with which medications were placed into the red, yellow, or green bins. The study found that desvenlafaxine and ziprasidone, neither of which has CYP2D6 mediated metabolism was in the green bin 100% of the time. Medications that were approximately equally metabolized by CYP and non-CYP enzymes were in the green bin between 84% and 95% of the time. Drugs that were heavily reliant on the CYP system, such as amitriptyline, which relies heavily on CYP2D6, were in the red bin frequently.

The authors suggest that a study comparing drug selection based on oxidative drug metabolism (i.e. information found in a medical reference) vs. pharmacogenetic testing could yield similar results.

We have reviewed the literature and found that no such comparison has actually been published.

NeuroIDGenetix

NeuroIDGenetix is a test that identifies pharmacokinetically or pharmacodynamically significant variants in the following 10 genes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, COMT, HTR2A, MTHFR. The test also incorporates information about other medications and lifestyle factors.

A randomized controlled trial was performed²³, in which 685 patients with depression were randomized to be treated either using the NeuroIDGenetix test or treated as usual without this test.

This study was registered at clinicaltrials.gov, (under the number NCT02878928 according to the manuscript) prior to the study, and the primary outcome given at the time of study registration was "The Reduction of Adverse Drug Events" at 12 weeks. Secondary outcomes considered were things like response of mood symptoms. While the manuscript does not explicitly review the primary and secondary outcomes, the manuscript notes no difference in adverse events; as such this study did not meet its primary outcome measure.

Additionally, the secondary endpoints reported in the manuscript diverge slightly from the outcomes pre-specified in clinicaltrials.gov. The secondary outcomes listed at Clinicaltrials.gov explicitly describe numeric values (continuous and threshold-based), outcome measures (HAM-A and HAM-D), and time (12 weeks). However, this study does not actually analyze these outcomes for the full group of patients in the study. Rather it sub-categorizes the population in ways not pre-specified at clinicaltrials.gov, and did not find a statistically significant difference in response for all subgroups.

Meta-analysis of Combinatorial Tests

We found two meta-analyses which significant overlapped in the studies reviewed, the statistical techniques, and the results. Both meta-analyses included studies which are all individually reviewed 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,²⁴ pooled the results of 6 studies and found a pooled relative risk for treatment remission of 1.71 in favor of pharmacogenomic testing, and a relative risk of 1.36 for remission, also favoring testing. A more recent meta-analysis by Bousman et al²⁵ included 5 studies and found a pooled relative risk for treatment remission of 1.74 in favor of pharmacogenomic 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.

Subject Matter Panel and Carrier Advisory Committee Meeting on June 26th, 2019

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 over the phone. While only invited experts and CAC members could speak, interested members of the public who registered could listen. The full recording is also available.²⁶ 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 pharmacogenomics testing generally speaking has the ability to provide clinically utile information that allows treating clinicians to select and dose particular medications appropriately. Pharmacogenomic 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) for particular genes has role in medication dosing and selection. The panel members did not specifically recommend or support the use of any one combinatorial pharmacogenomics test over another. There was general agreement that combinatorial pharmacogenomics 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 pharmacogenomics test provides information that improves outcomes more than single gene or multi-gene panels. Additionally, one subject matter expert commented that ultimately panels that simultaneously evaluate multiple genes will be necessary to effectively use panels to guide treatment for personalized drug selection. While it was not discussed by the panel, a manuscript submitted by Dr. Black did a retrospective comparison (using statistical modeling rather than a direct comparison) of GeneSight® to single gene testing.²⁷ This study suggested that combinatorial testing predicts poor antidepressant response and outcomes better than single gene testing. Two gene panels were not considered.

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

Additional Expert Input

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, 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 is whether the power of combinatorial pharmacogenomics is driven by a few genes or if it is absolutely due to the combinatorial effects." He indicated that for panel testing, he would recommend a minimum panel in psychiatry consisting 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 genes 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 CYPs. 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’s comments are summarized below.

Limitations of pharmacogenomics testing

A number of opinion leaders and experts representing multiple provider types have articulated how pharmacogenomics can be used, and how it might drive prescribing decisions, other thought leaders have called into question the utility of pharmacogenomics or specific tests in pharmacogenomics. Notably, the American Psychiatric Association, which is one of the largest organizations in the country representing treating clinicians with medication prescribing authority has to date published no position statement, guideline, or evidentiary interpretation.

The Food and Drug Administration (FDA) has published a document raising concerns about pharmacogenomics testing.²⁸ 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.

A manuscript examining the metascience of pharmacogenomics testing and providing an accompanying viewpoint reviewed 10 clinical studies of pharmacogenomics in psychiatry and found that none of them were blinded and used a protocol-based comparison.²⁹ 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 author’s 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.^{10,30,31} 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.

Dr. Bruce M. Cohen, the Director of the Program for Neuropsychiatric Research at McLean Hospital and Harvard Medical School, who submitted indicated that current pharmacogenetic 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.^{28,29} He also pointed out that, should a clinician be unsure about drug choice, a psychiatry consultation costs substantially less money than pharmacogenetic testing.

Guidelines and Supporting Information

A review of PharmGKB's database of annotations regarding 102 drugs from 3 guidelines³², shows that the majority of neuro-/psychiatric medications for which dosing pharmacogenomics dosing guidelines are available have them for CYP2D6.

Reference information may be used to generate a laboratory test report that is useful and interpretable, but the provision of reference information such as textbooks, databases, or software to a treating clinician is in itself is not a coverable benefit. Therefore, when considering coverage of a test, it is important to ascertain whether the data created from the analysis of a biological sample in the patient for whom a test is ordered is integral to the test result and report. The prominence of CYP2D6 in drug metabolism pathways indicates that, as the recent evidence appraisal notes³³, CYP2D6 is an appropriate comparator for control groups in comparative studies evaluating the benefit of combinatorial pharmacogenomics tests.

Analysis of Evidence (Rationale for Determination)

Level of Evidence

Quality of Evidence – Limited

Strength of Evidence – Limited

Weight of Evidence - Limited

Numerous prior Medicare coverage decisions have considered the evidence in the hierarchical framework of Fryback and Thornbury³⁴ where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. To apply this same hierarchical framework to analyze an in vitro diagnostic test, we utilized the ACCE Model Process for Evaluating Genetic Tests.³⁵ The practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes. When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

Combinatorial pharmacogenomic tests have been developed to help clinicians select medications and medication dosages. The evidence is insufficient to suggest that these tests provide a benefit beyond the benefit that would be achieved by testing a two gene panel consisting of CYP2C19 and CYP2D6. Additionally, the FDA has released a cautionary statement regarding these tests, and these tests are currently not recommended for use by the American Psychiatric Association, a major body representing clinicians who would be the treating physicians using such tests to

make treatment decisions.

In summary, while combinatorial pharmacogenomics tests have been developed to serve a vulnerable population, there is insufficient evidence to suggest that they offer a benefit above and beyond either informed prescribing or a single CYP gene test for CYP2D6 polymorphisms. MolDX recognizes that the field of personalized medicine is rapidly evolving, so this coverage decision will continue to be reassessed, and it may be revised or rescinded as new evidence emerges.

Finally, for the tests for which outcomes data is available, it is unclear how well the Medicare population is represented, given that the samples tend to be younger patients without significant comorbid disease.

Proposed Process Information

Synopsis of Changes

CHANGES	FIELDS CHANGED
This LCD was revised following an updated review of the evidence. Coverage criteria have been updated based on this evidence review, and coverage indications for another test were added. The title was also revised from MolDX: GeneSight® Assay for Refractory Depression to MolDX: Combinatorial Pharmacogenomics Limited Coverage.	N/A

Associated Information

N/A

Sources of Information

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Open Meetings

MEETING DATE	MEETING STATE(S)	MEETING INFORMATION
10/07/2019	South Carolina	Columbia

Contractor Advisory Committee (CAC) Meetings

N/A

MAC Meeting Information URL(s)

N/A

Proposed LCD Posting Date

08/22/2019

Comment Period Start Date

10/07/2019

Comment Period End Date

11/21/2019

Released to Final LCD Date

Please Note: This is not the LCD Effective Date.

N/A

Reason for Proposed LCD

- Provider Education/Guidance

Proposed Contact

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Coding Information

Proposed LCD

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

CPT/HCPCS Codes

Group 1 Paragraph:

N/A

Group 1 Codes:

CODE	DESCRIPTION
81479	UNLISTED MOLECULAR PATHOLOGY PROCEDURE

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

N/A

Group 1 Codes:

ICD-10 CODE	DESCRIPTION
F32.1	Major depressive disorder, single episode, moderate

ICD-10 CODE	DESCRIPTION
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.9	Major depressive disorder, single episode, unspecified
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.40	Major depressive disorder, recurrent, in remission, unspecified
F33.41	Major depressive disorder, recurrent, in partial remission
F33.9	Major depressive disorder, recurrent, unspecified

ICD-10 Codes that DO NOT Support Medical Necessity

N/A

Additional ICD-10 Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

N/A

Related National Coverage Documents

N/A

Keywords

N/A