2.04.72	Gene Expression Testing to Predict Coronary Artery Disease	
Section 2.0 Medicine	**Effective Date** August 29, 2014	
Subsection 2.04 Pathology/Laboratory	**Original Policy Date** October 5, 2012	**Next Review Date** August 2015

Description

The expression levels of various genes in circulating white blood cell or whole blood samples have been reported to discriminate between cases of obstructive coronary artery disease (CAD) and healthy controls. Multiplex gene expression testing can be combined with other risk factors to predict the likelihood of obstructive CAD in patients who present with chest pain or other suggestive symptoms, or in asymptomatic patients who are at high risk of CAD.

Related Policies

None

Policy

Gene expression testing to predict coronary artery disease (CAD) is considered **investigational** for all indications, including but not limited to prediction of the likelihood of CAD in stable, non-diabetic patients.

Policy Guidelines

There is no specific coding for this testing. It may be reported with the following unlisted CPT code:

- **81599**: Unlisted multianalyte assay with algorithmic analysis

Before 2013, the unlisted chemistry code 84999 would probably have been used. Palmetto GBA also currently recommends the use of code 84999 for this test on Medicare claims.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's

contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background

Heart disease is the leading cause of death in the U.S. and, together with cerebrovascular disease, accounted for 31% of deaths in 2007. (1) Patients with signs and symptoms of obstructive coronary artery disease (CAD), the result of a chronic inflammatory process that ultimately results in progressive luminal narrowing and acute coronary syndromes, may be evaluated with a variety of tests according to prior risk. Coronary angiography is the criterion standard for diagnosing obstructive CAD, but it is invasive and associated with a low but finite risk of harm. Thus, coronary angiography is recommended for patients at a high prior risk of CAD according to history, physical findings, electrocardiogram, and biomarkers of cardiac injury.(2) For patients initially assessed at low to intermediate risk, observation and noninvasive diagnostic methods, which may include imaging methods such as coronary computed tomographic angiography (CTA), may be recommended. Nevertheless, even noninvasive imaging methods have potential risks of exposure to radiation and contrast material. In addition, coronary angiography has a relatively low yield, despite risk stratification recommendations. In 1 study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial or branch vessel that was more than 2.0 mm in diameter; result was 41% if using the broader definition, stenosis of 50% or more in any coronary vessel).(3) Thus, methods of improving patient risk prediction before diagnostic testing are needed.

A CAD classifier has been developed based on expression levels, in whole blood samples, of 23 genes plus patient age and sex. This information is combined in an algorithm to produce a score from 1 to 40, with higher values associated with a higher likelihood of obstructive CAD. The test is marketed as Corus CAD™ (CardioDx Inc., Palo Alto, California). The intended population is stable, nondiabetic patients suspected of CAD either because of symptoms, a high-risk history, or a recent positive or inconclusive test result by conventional methods.

Regulatory Status

The Corus CAD™ test is not a manufactured test kit and has not been reviewed by the U.S. Food and Drug Administration. Rather, it is a laboratory-developed test, offered by the Clinical Laboratory Improvement Act- licensed CardioDx Commercial Laboratory.

Literature Review

What is the technical performance of the prediction model (assay development and validation)?

Assay Development. In an initial proof-of-principle study, Wingrove et al. evaluated 27 cases with and 14 controls without angiographically defined coronary artery disease (CAD) for expression of genes that differed significantly between the 2 groups, selecting

50 genes.(4) To that the authors added 56 genes selected from relevant literature reports and evaluated expression of these 106 genes in an independent set of 63 cases and 32 controls, resulting in the selection of 14 genes that independently and significantly discriminated between groups in multivariable analysis. The significance of 11 of these 14 genes was replicated in a third set of 86 cases and 21 controls. Expression of the 14 genes was proportional to maximal coronary artery stenosis in the combined cohort of 215 patients. Limitations of this study included variable source of RNA for different cohorts (whole blood vs. separated whole blood leukocytes), small sample sizes compared with large numbers of genes investigated, no apparent correction for multiple tests in significance testing, and modest discrimination between groups.

Elashoff et al. described final test development. (5) Investigators conducted 2 successive case-control gene expression discovery studies using samples from independent cohorts. Cases were angiographically defined as 75% or greater maximum stenosis in 1 major vessel, or 50% or greater in 2 vessels, and controls defined as less than 25% stenosis in all major vessels. Of clinical factors, diabetes had the most significant effect on gene expression; in the first case-control study (n=195), expression of 42 genes in nondiabetic patients and 12 genes in diabetic patients was found to significantly ($p<0.05$) discriminate between cases and controls with no overlap. As a result, the second case-control study (n=198) and final development of the assay was limited to nondiabetic patients. Final variable selection comprised the expression of 20 CAD-associated genes, 3 normalization genes, and terms for age and sex, all incorporated into an algorithm that resulted in an obstructive CAD score ranging from 1 to 40. Receiver-operating characteristic (ROC) analysis in the second case-control study resulted in an area under the curve (AUC) for CAD of 0.77 (95% confidence interval [CI]: 0.73 to 0.81).

Assay Validation. The finalized assay was validated in a prospective multicenter trial, the PREDICT trial, in which blood samples were collected from nondiabetic patients (n=526) with a clinical indication for coronary angiography but no known previous myocardial infarction (MI), revascularization, or obstructive CAD.(6) This is the same cohort from which the second assay development case-control cohort was drawn. (5) Patients were sequentially allocated to development and validation sets. The authors defined obstructive CAD as 50% or greater stenosis in 1 or more major coronary arteries on quantitative coronary angiography, which they stated corresponded to 65% to 70% stenosis on clinical angiography. The assay AUC for CAD was 0.70±0.02 ($p<0.001$).

What is the predictive ability of the test compared with alternative methods of predicting CAD?

The PREDICT trial compared the predictive accuracy of the GES measure with clinical predictors and myocardial perfusion imaging (MPI) stress testing.(5-7) This was a multicenter study of 1160 patients presenting for coronary angiography. All patients underwent Gene Expression Score (GES) assessment. Outcomes of interest were CAD at initial angiography and cardiac events, including revascularization, in the year after the initial angiogram.

The clinical predictor was the Diamond–Forrester clinical risk score, which had an AUC for CAD of 0.66; the combined AUC for clinical prediction and GES was 0.72 ($p=0.003$). MPI was performed on 310 patients (27%); AUC for the assay algorithm score plus MPI versus MPI alone was 0.70 versus 0.43 ($p<0.001$). Sensitivity and specificity calculated for a disease likelihood of 20% were 85% and 43%, respectively, corresponding to negative (NPV) and positive predictive values (PPV) of 83% and 46%, respectively. Average scores for patients with and without obstructive CAD were 25 and 17, respectively; assay algorithm scores increased with increasing degree of stenosis by angiography, with score distributions overlapping considerably.

The authors conducted a reclassification analysis, in which patients were first classified by either the Diamond- Forrester clinical risk score or an expanded clinical model based on routine history and clinical evaluation, then reclassified by the assay algorithm score. Net reclassification improvement, which quantitates the difference between the proportion of patients who are correctly reclassified from an incorrect initial classification and the proportion who are incorrectly reclassified from a correct initial classification, was 20% (p<0.001) using the initial Diamond-Forrester clinical risk score and 16% (p<0.001) using the expanded clinical model.

A follow-up publication from the PREDICT trial was published in 2012.(7) Rosenberg et al. reported on the association of GES with subsequent major adverse cardiac events (MACE), including MI, stroke/TIA (transient ischemic attack), all-cause mortality, and coronary revascularization. Among 1160 patients who underwent angiography in the PREDICT trial, there were 17 total MACE events (1.5%), 15 of which occurred 30 days or more after the initial angiogram. Using a GES cutoff of 15 or less, sensitivity for diagnosis of subsequent MACE was 82% and specificity was 34%. PPVs and NPVs were 1.8% and greater than 99%, respectively (with an overall MACE prevalence of 1.5%). The odds ratio (OR) for having an event was increased for patients with GES greater than 15, but this result did not reach statistical significance (OR=2.41; 95% CI: 0.74 to 10.5; p=0.16).

In another follow-up publication from the PREDICT trial, Lansky et al. (2012) found that GES was an independent predictor of CAD in multivariate analysis with ORs of 2.53 (p=0.001) for the total study population and 1.99 (p=0.001) and 3.45 (p=0.001) for males and females, respectively. (8) In this analysis, MPI was not associated with any measures of CAD in the general population or when stratified by gender. For every 10-point increase in GES, there was a corresponding 2-fold increase in odds of CAD and increases in maximum percent stenosis, number of lesions, and total plaque volume.

Thomas et al. (2013) assessed the clinical validity and utility of the Corus CAD™ for detection of obstructive CAD in nondiabetic patients in a multicenter, prospective study (COMPASS).(9) Obstructive CAD was defined as 50% or greater stenosis in 1 or more major coronary arteries on quantitative coronary angiography. The COMPASS patient sample differed from the PREDICT sample by including patients who had received a referral for MPI but had not been referred for invasive coronary angiography (ICA). Peripheral blood was drawn from all participants before MPI to obtain a GES. MPI-positive participants underwent ICA based on the clinician's judgment, and all other participants received coronary computed tomography angiography (CTA). Of 537 enrolled patients, only 431 (80.3%) were evaluable primarily due to refusal to undergo ICA or CTA. Follow-up was 6 months after testing, with clinical end points of MACE and revascularization. Using a GES cutoff of 15 or less, sensitivity and specificity of the Corus CAD™ test were 89% and 52%, respectively. A summary of the AUC, sensitivity, and specificity of comparators is given in Table 1. Net reclassification improvement in predicting CAD for GES compared with MPI (site-read), MPI (core-lab), Diamond-Forrester classification, and Morise score was 26%, 11%, 28%, and 60%, respectively.

Table 1. Summary of Gene Expression Score, Myocardial Perfusion Imaging, and Clinical Factor Algorithms for Detecting Obstructive CAD (9)[a]

Variable	GES	MPI (site-read)	MPI (core-lab)	Diamond-Forrester	Morise
N	431	431	371	430	431
ROC AUC (95% CI)	0.79 (0.72 to 0.84)	0.59 (0.54 to 0.65)	0.63 (0.57 to 0.70)	0.69 (0.62 to 0.75)	0.65 (0.59 to 0.74)

Sensitivity (95% CI), %	89 (78 to 95)	27 (17 to 40)	36 (24 to 50)	NR	NR
Specificity (95% CI), %	52 (47 to 57)	92 (88 to 94)	90 (87 to 93)	NR	NR
NPV (95% CI), %	96 (93 to 99)	88 (84 to 91)	88 (84 to 92)	NR	NR
PPV (95% CI), %	24 (19 to 30)	35 (22 to 51)	41 (28 to 56)	NR	NR
NRI, %	NA	26	11	28	60
ROC AUC for GES and second modality combined (95% CI)	NA	0.81 (0.76 to 0.86)	0.81 (0.76 to 0.87)	0.79 (0.73 to 0.85)	0.81 (0.75 to 0.89)

GES: Gene Expression Score; MPI: myocardial perfusion imaging; NA: not applicable; NPV: negative predictive value; NR: not reported; NRI: net reclassification improvement; PPV: positive predictive value; ROC AUC: area under the receiver-operator characteristic curve.

[a] Obstructive CAD was defined as ≥50% stenosis in 1 or more major coronary arteries on quantitative coronary angiography.

Twenty-eight adverse events were observed: 25 revascularizations within 30 days, 2 MACE, and 1 further revascularization. Twenty-five of 26 patients who underwent revascularization and both MACE patients had high GES (>15). GES was associated with MACE and revascularization in a logistic regression model (p<0.001) with a sensitivity of 96% and a NPV of 99% at a score threshold of 15. The GES test also was correlated with maximum percent stenosis (*r*=0.46, p<0.001).

Voros et al. (2013) pooled results from PREDICT and COMPASS to compare GES with CT imaging for detecting plaque burden (coronary artery calcium [CAC]), and luminal stenosis. (10) Six hundred ten patients, 216 from PREDICT (19% of enrolled patients) and 394 from COMPASS (73% of enrolled patients), who had undergone CAC scoring; CTA, and GES were included. (SD) age was 57 (11) years; 50% were female, and approximately 50% used statin medication. Prevalence of obstructive CAD (≥50% stenosis) was 16% in the PREDICT cohort (patients referred for coronary angiography) and 13% in the COMPASS cohort (patients referred for MPI). In linear regression analyses, GES was statistically significantly correlated with CAC (*r*=0.50), the number of arterial segments with any plaque (*r*=0.37), overall stenosis severity (*r*=0.38), and maximum luminal stenosis (*r*=0.41) (all p<0.01), but strength of correlations was modest. Several GES cutoffs were explored (e.g., to maximize diagnostic accuracy). Results using a cutoff of 15 points are shown in Table 2. For detecting luminal stenosis of 50% or greater, GES PPV and NPV were 0.23 and 0.95, respectively. For detecting clinically significant CAC (≥400), GES PPV and NPV were 0.14 and 0.97, respectively. Limitations of the study included lack of clinical outcomes (e.g., survival, morbidity), and lack of comparison with CAC and CTA for predicting these outcomes (i.e., incremental predictive value of GES was not assessed).

Table 2. Performance of Gene Expression Score and Diamond-Forrester Classification for Coronary Artery Plaque Burden and Luminal Stenosis (10)

Outcome	GES ROC AUC (95% CI)	Diamond-Forrester ROC AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
Plaque burden[a]						
CAC >0	0.75 (0.71 to 0.79)	0.65 (0.61 to 0.69)	0.71	0.62	0.65	0.68
CAC ≥400	0.75 (0.68 to 0.82)	0.61 (0.53 to 0.69)	0.84	0.49	0.14	0.97

Luminal stenosis by CT angiography						
≥50%	0.75 (0.70 to 0.80)	0.65 (0.59 to 0.71)	0.84	0.51	0.23	0.95
≥70%	0.75 (0.67 to 0.83)	0.63 (0.53 to 0.73)	0.90	0.48	0.08	0.99

CAC: coronary artery calcium; CT: computed tomography; GES: Gene Expression Score; NPV: negative predictive value; PPV: positive predictive value; ROC AUC: area under the receiver-operator characteristic curve.

[a] Long-term outcomes are generally excellent in patients with zero CAC and substantially worse in patients with CAC greater than 400.

Section summary

Results of the PREDICT and COMPASS studies established that GES has predictive ability for CAD. The PREDICT and COMPASS studies reported that GES is superior to the Diamond-Forrester model and to MPI for predicting CAD. However, there are several limitations to the evidence on comparative predictive accuracy. In the PREDICT study, the assay algorithm score discriminated cases from controls significantly better than the Diamond–Forrester clinical score by AUC analysis; however it did not discriminate better than an expanded clinical model without family history or electrocardiogram (AUC, 0.745 vs. 0.732, respectively; p=0.089). Additionally, neither Diamond-Forrester clinical risk score nor the expanded clinical model included family history or electrocardiogram results, which might increase accuracy of the initial classification and decrease the net reclassification improvement observed. Furthermore, the Diamond-Forrester model is a simple prediction rule that is not commonly used in clinical care. The Framingham risk score would be a more relevant comparator that is part of contemporary clinical care. Finally, modest correlations of GES with coronary artery plaque burden and luminal stenosis in the absence of clinical outcomes are of uncertain clinical significance.

The COMPASS study compared GES with results from MPI stress testing. In that trial, sensitivity of MPI was low at 27%. This is considerably lower than is routinely reported in the literature. For example, in a meta- analysis performed in support of ACC/AHA guidelines on MPI, sensitivity was estimated at 87% to 89%.(11) This raises the question of whether accuracy of MPI in the COMPASS study was representative of that seen in current clinical care. Also, the comparison of overall accuracy of GES with MPI testing does not establish that clinical decisions would be changed, specifically whether patients with a positive MPI could safely forego further invasive testing based on a low GES.

Does use of the test lead to changes in management that improve outcomes?

The IMPACT-CARD study compared a prospective cohort with matched historical controls to evaluate whether the GES test altered the cardiologist's evaluation and clinical management of CAD. (12) CAD was categorized by the authors as no CAD (0% stenosis), CAD (≤50% stenosis) or CAD (>50% stenosis). All participants were nondiabetic, had no known prior MI or revascularization, were not using steroids, immune suppressive agents or chemotherapeutic agents, and had been referred to a cardiologist for evaluation of chest pain or angina equivalent symptoms. Eighty-eight patients were enrolled and 83 included in the final analysis. The matched cohort comprised 83 patients selected with similar distributions of age, gender, and clinical risk factors, and had been evaluated at a participating clinic within the past 3 to 30 months.

In a similar but unmatched study, IMPACT-PCP evaluated whether GES altered primary care providers' diagnostic evaluation and clinical management of stable, nonacute, nondiabetic patients presenting with CAD symptoms.(13) Nine primary care providers at 4

centers evaluated 261 consecutive patients, 251 (96%) of whom were eligible for participation. Clinicians documented their pretest impressions and recommendations for further evaluation and management on a clinical report form. All patients underwent GES testing. The primary outcome was the change in patient management between preliminary and final treatment plans.

In both studies, change in patient management was defined prospectively as an increase or decrease in intensity of the diagnostic plan. The authors defined categories of intensity in the following order: (1) no further cardiac testing or medical therapy for angina or noncardiac chest pain, (2) stress testing (with/without imaging) or CTA, or (3) ICA. GESs were divided into a high-risk group (>15) and a low-risk group (≤15). In IMPACT-CARD, diagnostic testing plans were changed for 58% of patients in the prospective cohort (95% CI: 46 to 69; p<0.001) with a greater reduction in testing intensity (39%) compared with increased testing intensity (19%). Compared with the historical control group, the prospective cohort had a 71% reduction in overall diagnostic testing (p<0.001). Results from IMPACT-PCP were similar: Diagnostic testing plans were changed for 58% of patients, with reductions in testing intensity more common than increases (64% vs. 34%; p<0.001). No study- related major adverse cardiovascular events were observed in 247 patients (98%) who had at least 30 days of follow-up.

A secondary analysis of IMPACT-CARD examined testing patterns around ICA. Thirty patients, 14 from the prospective cohort and 16 from the historical cohort, who underwent ICA, were included in the analysis. The authors did not find a significant difference in diagnostic yield between the 2 groups (p=0.24). No major cardiovascular adverse events were observed for either cohort during the 6-month follow-up period.

The REGISTRY 1 study assessed the impact of GES on patient management decisions by examining the association between GES test results and post-test referral patterns. (14) Primary care practitioners at 7 centers evaluated 342 stable, nonacute, nondiabetic patients presenting with CAD symptoms. All patients underwent GES testing. Of 167 patients with low (≤15) GES, 10 (6%) were referred for further cardiac evaluation compared with 122 (70%) of 175 patients in the high GES group (p<0.001). Analysis of GES as a continuous variable showed a statistically significant change in cardiac referrals for every 10-point change in GES (adjusted OR, 13.7; 95% CI: 12.5 to 15.0; p<0.001). Over a mean follow-up of 264 days, there were 5 major adverse cardiovascular events, 2 in the low GES group and 3 in the high GES group. Of 21 patients who underwent elective ICA, 1 (50%) of 2 in the low GES group and 8 (42%) of 19 in the high GES group had obstructive findings.

Section summary

Based on the IMPACT and REGISTER 1 studies, management decisions may be changed as a result of GES. IMPACT-CARD was limited by comparison with historical controls, which were not well-matched to the study population, and IMPACT-PCP was an uncontrolled study. In addition, the impact of management changes in these studies is uncertain. There is no information provided on whether management changes led to beneficial effects on outcome, and it is not possible to estimate the likelihood of benefit from the information given. Although REGISTER 1 followed patients for approximately 9 months, reported clinical outcomes do not indicate benefits of GES testing. Therefore, it is not possible to conclude that GES leads to changes in management that improve outcomes.

Ongoing Clinical Trials

CardioDX is establishing the PRESET registry to evaluate patterns of care associated with the use of Corus® CAD in real-world clinical care settings (NCT01677156). Adults who present to their primary clinician's office with chest pain suggesting obstructive CAD are

eligible. Patients with a history of CAD, including previous MI, New York Heart Association class 3 or 4 heart failure, or diabetes mellitus are excluded. Estimated enrollment is 1000 patients, and study completion is expected in March 2015.

Summary

Gene expression assays to predict the likelihood of obstructive coronary artery disease (CAD) have potential to improve the accuracy of predicting CAD likelihood. A commercially available gene expression score (GES) test, Corus CAD™, has been developed and validated for this purpose in nondiabetic patients. The PREDICT study raised the possibility that this test could be used to increase the proportion of patients selected for coronary angiography who truly have disease and reduce the number of patients who might otherwise be inappropriately exposed to radiation, contrast agent, and an invasive procedure. Results of initial validation studies reported

that the test may improve CAD prediction beyond that of simple prediction models such as Diamond-Forrester, but the improvement in CAD prediction when added to routine clinical evaluation is uncertain. The test also has been shown to have some predictive ability for future cardiac events and revascularization. In the COMPASS study, overall accuracy of GES in predicting cardiac events was superior to myocardial perfusion imaging (MPI) in patients who were referred for MPI testing. However, in that study, reported sensitivity of MPI was considerably lower than generally reported in the literature. Also, it is unclear from the COMPASS study whether patients with a positive MPI could safely forego further testing based on a low GES.

Clinical utility of GES has not been demonstrated. Three studies with methodologic limitations reported management changes as a result of the test, but the effect of these management changes is uncertain. Currently, there is no convincing evidence that the use of GES can reduce unnecessary coronary angiography. As a result, the use of gene expression scores for predicting CAD is considered investigational.

Practice Guidelines and Position Statements

American Heart Association

In 2012, the American Heart Association (AHA) released a policy statement on genetics and cardiovascular disease. (15) Gene expression testing is not specifically mentioned. Generally, the writing committee supported recommendations issued in 2000 by a now defunct Advisory Committee to the Department of Health and Human Services, which stated, "No test should be introduced in the market before it is established that it can be used to diagnose and/or predict a health-related condition in an appropriate way."(16)

Medicare National Coverage

There are no Medicare National Coverage Determinations for GES testing to predict CAD. In July 2013, Palmetto GBA, the Medicare contractor in California, issued a positive local coverage decision for the CorusCAD® test in patients who have typical symptoms of CAD or atypical symptoms and 1 or more CAD risk factors. Because all CorusCAD® tests are processed in California, the test will be covered for Medicare patients in the United States.

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Documentation Required for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE

The following services are considered investigational and therefore not covered for any indication.

Type	Code	Description
CPT	***See Policy Guidelines***	
	81599	Unlisted multianalyte assay with algorithmic analysis
	84999	Unlisted chemistry procedure
HCPC	None	
ICD9 Procedure	None	
ICD10	***For dates of service on or after 10/01/2015***	

Type	Code	Description
Procedure	None	
ICD9 Diagnosis	All Diagnoses	
ICD10 Diagnosis	***For dates of service on or after 10/01/2015***	
	Z13.6	Encounter for screening for cardiovascular disorders
	Z15.89	Genetic susceptibility to other disease

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/5/2012	BCBSA Medical Policy adoption	Medical Policy Committee
8/29/2014	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.