



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy is addressed separately in medical policy 00284.

Note: Genotyping for 9p21 Single-Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm is addressed separately in medical policy 00299.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers gene expression testing in the evaluation of patients with stable ischemic heart disease for all indications, including but not limited to prediction of coronary artery disease (CAD) in stable, nondiabetic patients to be **investigational**.*

Background/Overview

Heart disease is the leading cause of death in the United States. Patients with signs and symptoms of obstructive CAD 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. 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, may be recommended. Nevertheless, some 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 a study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, $\geq 50\%$ stenosis of the diameter of the left main coronary artery or $\geq 70\%$ stenosis of the diameter of a major epicardial or branch vessel that was >2.0 mm in diameter and 41% if using the broader definition, $\geq 50\%$ stenosis in any coronary vessel). Thus, methods of improving patient risk prediction before invasive coronary angiography (ICA) are needed.

In an initial proof-of-principle study of the Gene Expression Score (GES) test in patients referred for ICA, Wingrove et al (2008) evaluated 27 cases (96% symptomatic) with and 14 controls without angiographically defined CAD for expression of genes that differed significantly between the 2 groups, selecting 50 genes. To that 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

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

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.

Elashoff et al (2011) described final test development of the GES. 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 in symptomatic patients (CATHGEN; 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, in a subset of 198 patients from the prospective PREDICT study (discussed next), and final development of the assay was limited to nondiabetic patients (62% symptomatic). 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 analysis in PREDICT resulted in an area under the curve for CAD of 0.77 (95% confidence interval, 0.73 to 0.81).

A CAD classifier has been developed based on expression levels derived from the previously described studies, in whole blood samples, of 23 genes plus patient age and sex. This information is used 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. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The Corus CADTM test (CardioDx, Palo Alto, CA) is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

There are no Medicare national coverage determinations for GES testing to predict CAD. In July 2013, Palmetto GBA issued a positive local coverage decision for the Corus CAD test in patients who have typical symptoms of CAD or atypical symptoms and 1 or more CAD risk factors.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

Rationale/Source

See the Appendix Table 1 for genetic testing categories.

Validation of the clinical use of any genetic or gene expression test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of a test in detecting a mutation that is present or in excluding a mutation that is absent; (2) clinical validity, which refers to the diagnostic performance of a test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

ANALYTIC VALIDITY

We did not identify any studies evaluating the analytic validity of the GES test.

CLINICAL VALIDITY

A GES was validated in the prospective multicenter PREDICT study in which blood samples were collected from 526 nondiabetic patients with a clinical indication for coronary angiography but no known previous myocardial infarction (MI), revascularization, or obstructive CAD; 71% symptomatic. This is the same cohort from which the second assay development case-control cohort was drawn. Patients were sequentially allocated to development and validation sets. Investigators 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 area under the curve (AUC) for CAD was 0.70 ± 0.02 ($p < 0.001$). In a 2014 follow-up publication, Investigators evaluated GES performance in nondiabetic patients from the gene discovery and algorithm development cohorts in combination with the validation cohort (N=1038) and, as would be expected, found similar performance (AUC, 0.70 ± 0.02 ; $p < 0.001$).

PREDICT compared the predictive accuracy of the GES test with clinical predictors and myocardial perfusion imaging (MPI) stress testing. This multicenter study included 1160 patients (development and validation cohorts combined) presenting for coronary angiography (71% symptomatic). All patients underwent 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 (27%) patients; AUC for the assay algorithm score plus MPI was 0.70 and 0.43 for MPI alone ($p < 0.001$). 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 greater degree of stenosis by angiography, with score distributions overlapping considerably.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

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 correctly reclassified from an incorrect initial classification and the proportion 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.

In 2012, Rosenberg et al published a follow-up report from PREDICT on the association between GES and 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 PREDICT, there were 17 (1.5%) MACE, 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 a GES greater than 15, but this result was not statistically significant (OR=2.41; 95% confidence interval [CI], 0.74 to 10.5; $p = 0.16$).

In another follow-up from PREDICT, Lansky et al (2012) found that the 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. In this analysis, MPI was not associated with any measures of CAD in the general population or when stratified by sex. For every 10-point increase in GES, there was a corresponding 2-fold increase in the 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 symptomatic, nondiabetic patients in a multicenter, prospective study (COMPASS). Obstructive CAD was defined as 50% or greater stenosis in 1 or more major coronary arteries on quantitative coronary angiography. The COMPASS sample base differed from the PREDICT sample by including patients who had received a referral for MPI but had not been referred for ICA. Peripheral blood was drawn from all participants before MPI to obtain a GES. MPI-positive participants underwent ICA based on clinician judgment, and all other participants received coronary computed tomography angiography (CTA). Of 537 enrolled patients, only 431 (80%) 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, the 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 rates in predicting CAD for GES compared with MPI (site-read), MPI (core-lab), Diamond-Forrester classification, and Morise score were 26%, 11%, 28%, and 60%, respectively.

Table 1. Summary of GES, MPI, and Clinical Factor Algorithms for Detecting Obstructive CAD^a

Variable	GES	MPI (site-read)	MPI (core-lab)	Diamond-Forrester	Morise
N	431	431	371	430	431
ROC AUC (95% CI)	0.79	0.59	0.63	0.69	0.65

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

	(0.72 to 0.84)	(0.54 to 0.65)	(0.57 to 0.70)	(0.62 to 0.75)	(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)

CAD: coronary artery disease; CI: confidence interval; 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 $\geq 50\%$ stenosis in ≥ 1 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 a high GES (>15). GES was associated with MACE and revascularization in a logistic regression model ($p < 0.001$), with a sensitivity of 96% and an NPV of 99% at a score threshold of 15. The GES test also correlated with maximum percent stenosis ($r = 0.46$, $p < 0.001$).

Voros et al (2014) pooled results from PREDICT and COMPASS to compare GES with computed tomography imaging for detecting plaque burden (coronary artery calcium [CAC]), and luminal stenosis. 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. Mean standard deviation (SD) age was 57 (11) years; 50% were female, and approximately 50% used statin medication. Prevalence of obstructive CAD ($\geq 50\%$ 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 statistically and 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 the strength of the 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, the GES PPV and NPV were 23% and 95%, respectively. For detecting clinically significant CAC (≥ 400), the GES PPV and NPV were 14% and 97%, respectively. Limitations of the study included a lack of clinical outcomes (e.g., survival, morbidity) and lack of comparison with CAC and CTA for predicting these outcomes (i.e., incremental GES predictive value was not assessed).

Table 2. Performance of GES and Diamond-Forrester Classification for Coronary Artery Plaque Burden and Luminal Stenosis: Pooled PREDICT and COMPASS Analysis

Outcome	GES ROC AUC (95% CI)	Diamond-Forrester ROC AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
Plaque burden [†]						
CAC > 0	0.75 (0.71 to 0.79)	0.65 (0.61 to 0.69)	0.71	0.62	0.65	0.68

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

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 CTA						
≥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

CI: confidence interval; CAC: coronary artery calcium; CTA: computed tomography angiography; GES: Gene Expression Score; NPV: negative predictive value; PPV: positive predictive value; ROC AUC: area under the receiver operating characteristic curve.

^a Long-term outcomes are generally excellent for patients with CAC >0 and substantially worse for patients with CAC >400.

Section Summary: Clinical Validity

The GES is correlated with the presence of CAD. The PREDICT and COMPASS studies reported that the 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 (AUC=0.745) or electrocardiogram (AUC=0.732; 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 not commonly used in clinical care to determine referral to coronary angiography. 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 symptomatic patients. In that study, the sensitivity of MPI was low (27%). This is considerably lower than what is routinely reported in the literature. For example, in a 2003 meta-analysis performed in support of American College of Cardiology and American Heart Association guidelines on MPI, sensitivity was estimated at 87% to 89%. This raises the question whether accuracy of MPI in the COMPASS study was representative of that seen in current clinical care or whether the spectrum of patients referred for MPI in the study was representative. Given the imperfect sensitivity and specificity of GES, and the known diagnostic characteristics of standard noninvasive tests for patients with stable ischemic heart disease, the diagnostic characteristics of GES do not by themselves obviously demonstrate that patient outcomes would be improved compared to standard diagnostic workup.

CLINICAL UTILITY

The clinical utility of the GES test would be established by demonstrating improved outcomes in patients managed with the test compared to patients managed without it, preferably in randomized controlled trials. Patients managed without the GES test should be evaluated according to established guidelines for the noninvasive evaluation of patients with stable ischemic heart disease.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

Studies examining patient outcomes of GES testing have either analyzed changes in physician management as an outcome or have not performed a rigorous comparative trial evaluating patient outcomes.

The IMPACT-CARD study (2013) compared a prospective cohort with matched historical controls to evaluate whether the GES test altered cardiologist evaluation and clinical management of CAD. CAD was categorized by authors as no CAD (0% stenosis), CAD ($\leq 50\%$ stenosis), or CAD ($>50\%$ stenosis). Eighty-eight patients were enrolled and 83 included in the final analysis. The matched cohort comprised 83 patients selected with similar distributions of age, sex, and clinical risk factors evaluated at a participating clinic within the past 3 to 30 months. 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 ($p < 0.001$).

IMPACT-PCP (2014) evaluated whether having the GES altered primary care providers' diagnostic evaluation and clinical management of stable, nonacute, nondiabetic patients presenting with CAD symptoms. 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. Diagnostic testing plans were changed for 58% of patients, with reductions in testing intensity more common (64%) than increases (34%; $p < 0.001$). No study-related MACE were observed in 247 (98%) patients who had at least 30 days of follow-up.

The REGISTRY 1 study (2015) assessed the impact of having the GES on patient management decisions by examining the association between GES results and posttest referral patterns. 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 MACE, 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.

Ladapo et al (2015) pooled results for women who participated in the IMPACT-PCP ($n=140$) and REGISTRY 1 ($n=180$) studies to evaluate the impact of GES on further cardiac evaluation ($N=320$). Referral rate for further cardiac evaluation was 4% for women with low GES ($n=248$) versus 83% for women with elevated GES ($n=72$). Overall, there were 4 MACE/revascularization events. (Median follow-up was 37 days in IMPACT-PCP and 278 days in REGISTRY 1.) Events per GES risk group were not reported.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

Section Summary: Clinical Utility

The studies of GES testing do not provide evidence of the clinical utility of this testing. Although physicians may have made management decisions based on results of GES testing, it is unknown whether the management decisions led to improved patient outcomes. There are no rigorous studies comparing outcomes for patients managed with GES testing versus alternative methods for stable ischemic heart disease. It is not clear that the diagnostic characteristics of GES, as established in the studies of clinical validity, would translate to improved patient outcomes through a chain of evidence.

SUMMARY OF EVIDENCE

For individuals who have suspected stable ischemic heart disease without diabetes who receive gene expression testing, the evidence includes retrospective case-control and prospective cohort studies. Relevant outcomes are test accuracy and validity, change in disease status. Results of initial validation studies have reported that the test may improve CAD prediction beyond that of simple prediction models (e.g., Diamond-Forrester), but the benefit of improved prediction when added to routine clinical evaluation is uncertain. The test also has been shown to have some predictive ability of future cardiac events and revascularization. In the COMPASS study, overall accuracy of the GES test in predicting cardiac events was superior to MPI in patients referred for MPI testing. However, in that study, the reported sensitivity of MPI was considerably lower than that generally reported in the literature. Also, it is unclear from the COMPASS study whether patients with positive MPI could safely forgo further testing based on a low GES. The clinical utility of the 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 on patient outcomes is uncertain. Evidence for a significant incremental improvement in outcomes when gene expression testing is added to standard clinical evaluation is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Gene Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease", 2.04.72, 1:2017.
2. Xu J, Kochanek KD, Murphy SL, et al. Deaths: final data for 2007. *Natl Vital Stat Rep*. May 2010;58(19):1-19. PMID 25075874
3. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. Dec 18 2012;60(24):e44-e164. PMID 23182125
4. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. Mar 11 2010;362(10):886-895. PMID 20220183
5. Wingrove JA, Daniels SE, Sehnert AJ, et al. Correlation of peripheral-blood gene expression with the extent of coronary artery stenosis. *Circ Cardiovasc Genet*. Oct 2008;1(1):31-38. PMID 20031539
6. Elashoff MR, Wingrove JA, Beineke P, et al. Development of a blood-based gene expression algorithm for assessment of obstructive coronary artery disease in non-diabetic patients. *BMC Med Genomics*. 2011;4(1):26. PMID 21443790
7. Rosenberg S, Elashoff MR, Beineke P, et al. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. *Ann Intern Med*. Oct 5 2010;153(7):425-434. PMID 20921541
8. Daniels SE, Beineke P, Rhees B, et al. Biological and analytical stability of a peripheral blood gene expression score for obstructive coronary artery disease in the PREDICT and COMPASS studies. *J Cardiovasc Transl Res*. Oct 2014;7(7):615-622. PMID 25119856

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

9. Rosenberg S, Elashoff MR, Lieu HD, et al. Whole Blood Gene Expression Testing for Coronary Artery Disease in Nondiabetic Patients: Major Adverse Cardiovascular Events and Interventions in the PREDICT Trial. *J Cardiovasc Transl Res.* Jun 2012;5(3):366-374. PMID 22396313
10. Lansky A, Elashoff MR, Ng V, et al. A gender-specific blood-based gene expression score for assessing obstructive coronary artery disease in nondiabetic patients: results of the Personalized Risk Evaluation and Diagnosis in the Coronary Tree (PREDICT) trial. *Am Heart J.* Sep 2012;164(3):320-326. PMID 22980297
11. Thomas GS, Voros S, McPherson JA, et al. A blood-based gene expression test for obstructive coronary artery disease tested in symptomatic nondiabetic patients referred for myocardial perfusion imaging the COMPASS study. *Circ Cardiovasc Genet.* Apr 2013;6(2):154-162. PMID 23418288
12. Voros S, Elashoff MR, Wingrove JA, et al. A peripheral blood gene expression score is associated with atherosclerotic plaque burden and stenosis by cardiovascular CT-angiography: results from the PREDICT and COMPASS studies. *Atherosclerosis.* Mar 2014;233(1):284-290. PMID 24529158
13. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation.* Sep 16 2003;108(11):1404-1418. PMID 12975245
14. McPherson JA, Davis K, Yau M, et al. The clinical utility of gene expression testing on the diagnostic evaluation of patients presenting to the cardiologist with symptoms of suspected obstructive coronary artery disease: results from the IMPACT (Investigation of a Molecular Personalized Coronary Gene Expression Test on Cardiology Practice Pattern) trial. *Crit Pathw Cardiol.* Jun 2013;12(2):37-42. PMID 23680805
15. Herman L, Froelich J, Kanelos D, et al. Utility of a genomic-based, personalized medicine test in patients presenting with symptoms suggesting coronary artery disease. *J Am Board Fam Med.* Mar-Apr 2014;27(2):258-267. PMID 24610188
16. Ladapo JA, Lyons H, Yau M, et al. Enhanced assessment of chest pain and related symptoms in the primary care setting through the use of a novel personalized medicine genomic test: results from a prospective registry study. *Am J Med Qual.* Jul-Aug 2015;30(4):345-352. PMID 24798176
17. Ladapo JA, Herman L, Weiner BH, et al. Use of a blood test incorporating age, sex, and gene expression influences medical decision-making in the evaluation of women presenting with symptoms suggestive of obstructive coronary artery disease: summary results from two ambulatory care studies in primary care. *Menopause.* Nov 2015;22(11):1224-1230. PMID 25828395
18. Ashley EA, Hershberger RE, Caleshu C, et al. Genetics and cardiovascular disease: a policy statement from the American Heart Association. *Circulation.* Jul 3 2012;126(1):142-157. PMID 22645291
19. National Institutes of Health. Office of Science Policy. Enhancing the oversight of genetic tests: recommendations of the Secretary's Advisory Committee on Genetic Testing (SACGT), July 2000. <http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/genetics-health-and-society-secretarys-advisory-committee-genetic-testing/enhancing-oversight-genetic-tests-recommendations-sacgt>. Accessed June 12, 2015.
20. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* Nov 04 2014;64(18):1929-1949. PMID 25077860

Policy History

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

- | | |
|------------|---|
| 07/07/2011 | Medical Policy Committee review |
| 07/20/2011 | Medical Policy Implementation Committee approval. New policy. |
| 06/28/2012 | Medical Policy Committee review |
| 07/27/2012 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/27/2013 | Medical Policy Committee review |
| 07/17/2013 | Medical Policy Implementation Committee approval. Added "for prediction of the likelihood of coronary artery disease (CAD) in stable, nondiabetic patients" to the investigational statement. |

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

07/10/2014 Medical Policy Committee review

07/16/2014 Medical Policy Implementation Committee approval. Format revision; including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

09/03/2015 Medical Policy Committee review

09/23/2015 Medical Policy Implementation Committee approval. Revised wording of INV statement.

12/01/2016 Medical Policy Committee review.

12/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

12/07/2017 Medical Policy Committee review.

12/20/2017 Medical Policy Implementation Committee approval. Title changed from "Gene Expression Testing to Predict Coronary Artery Disease" to "Gene Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease". Indication changed to "patients with stable ischemic heart disease" to be consistent with current guideline statements. Policy statement intent unchanged, but wording changed to reflect current terminology for indication.

Next Scheduled Review Date: 12/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479, 81493, 81599, 84999
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309

Original Effective Date: 07/20/2011

Current Effective Date: 12/20/2017

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

APPENDIX

Appendix Table 1. Categories of Genetic Testing

Category	Addressed
1. Testing of an affected individual's germline to benefit the individual	
1a. Diagnostic	X
1b. Prognostic	
1c. Therapeutic	
2. Testing cancer cells from an affected individual to benefit the individual	
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	
3. Testing an asymptomatic individual to determine future risk of disease	
4. Testing of an affected individual's germline to benefit family members	
5. Reproductive testing	
5a. Carrier testing: preconception	
5b. Carrier testing: prenatal	
5c. In utero testing: aneuploidy	
5d. In utero testing: mutations	
5e. In utero testing: other	
5f. Preimplantation testing with in vitro fertilization	

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.