Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm

Policy # 00299
Original Effective Date: 06/15/2011
Current Effective Date: 07/12/2021

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.

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 genotyping for *9p21* single nucleotide polymorphisms (SNPs) for all clinical uses including but not limited to, identification of patients who may be at increased risk of cardiovascular disease (CVD) or its manifestations (e.g., myocardial infarction [MI], ischemic stroke, peripheral arterial disease, coronary artery calcification), or identification of patients who may be at increased risk for aneurysmal disease (abdominal aortic aneurysms [AAAs], intracranial aneurysms, polypoidal choroidal vasculopathy) to be **investigational.***

Background/Overview

A number of highly correlated SNPs found at the 9p21 locus have been significantly associated with risk of MI, particularly early onset MI, and other manifestations of CVD. Associations between *9p21* SNPs and risk of AAA, intracranial aneurysms, and other vascular disorders have also been reported. Genotyping for *9p21* SNPs has been investigated to identify patients at risk of cardiovascular disorders.

In 2007, multiple investigators nearly simultaneously reported the first common genetic variant affecting the risk of coronary heart disease ([CHD] defined as inadequate circulation to cardiac muscle and surrounding tissue resulting in MI, unstable angina pectoris, coronary revascularization, or death) in whites through genome-wide association studies (GWAS) using SNP arrays. Additional studies identified other SNPs with similar estimates of CHD risk. These SNPs were confirmed in case control replication studies in a variety of study populations, showing that the identified SNPs were associated with CHD and even more specifically with MI. All of the SNPs were found within

a locus spanning a 58-kilobase region at chromosome 9p21.3 (thus the locus is sometimes represented more specifically as 9p21.3; for simplicity, 9p21 will be used for the rest of this document), are highly correlated (r^2>0.8) and thus are said to be in linkage disequilibrium (nonrandom association of alleles). The association of any identified SNP with CHD risk was shown to be independent of traditional risk factors.

Several studies have extended the 9p21 association to other vascular diseases including ischemic stroke; thus 9p21 may be reported as being associated with CVD (defined as CHD and cerebrovascular disease) outcomes. Associations have also been reported with AAA and with intracranial arterial aneurysm and other vascular diseases.

Several genes are found at the 9p21 locus, including ANRIL, which encodes a large noncoding ribonucleic acid (RNA) which may have regulatory functions, and *CDKN2A* and *CDKN2B*, which encode cyclin-dependent kinase inhibitors. The mechanisms by which the SNPs lead to increased CHD risk have been largely unknown. In 2011, Harismendy et al. identified several potential enhancer regulatory deoxyribonucleic acid (DNA) sequences in the 9p21 region. They reported that the SNP rs10747278, consistently associated with increased risk of CHD, occurs in 1 of these enhancer sequences and that the risk allele disrupts a transcription factor binding site involved in the inflammatory response (STAT1). The interaction of STAT1 with part of the inflammatory signaling pathway, interferon-gamma, is impaired in *9p21* risk carriers. Congrains et al. genotyped 18 SNPs across the CVD-associated region and encompassing *ANRIL* and *CDKN2A/B* to determine the impact of *9p21* variants on gene expression. The authors reported that "several SNPs in 9p21 locus affect the expression of *ANRIL*, which is further in control of the regulation of *CDKN2A/B* and cell growth. Cell proliferation mediates the progression of atherosclerosis and is also directly or indirectly involved in the pathogenesis of diseases associated with this locus."

Commercially Available Tests

Several laboratories offer 9p21 genotyping. For example, the Berkeley HeartLab (Quest Diagnostics) offers the 9p21 Genotype Test, which detects the rs10757278 A>G and rs1333049 G>C SNPs within the 9p21 locus of chromosome 9. Baylor Miraca Genetics Laboratories offers genotyping of the rs10757278 A>G polymorphism at *9p21*.

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Cardiac risk genotyping panels offered by other laboratories may include and individually report *9p21* SNP results. For example, the deCODE MI™‡ (deCODE Genetics, Reykjavik) test genotypes 9p21.3 rs10757278 in addition to 7 other SNPs from other chromosomal loci to estimate the risk of CHD and MI.

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). 9p21 genotyping tests are 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.

Rationale/Source

A number of highly correlated single-nucleotide polymorphisms (SNPs) found at the 9p21 locus have been significantly associated with risk of myocardial infarction (MI), particularly early-onset MI, and other manifestations of cardiovascular disease. Associations between *9p21* SNPs and risk of abdominal aortic aneurysm, intracranial aneurysms, and other vascular disorders have also been reported. Genotyping for *9p21* SNPs has been investigated to identify patients at risk of cardiovascular disorders.

The association of SNPs at the 9p21 locus with coronary artery/heart disease (CAD/CHD) outcomes (clinical validity) is well-established and consistent in multiple independent populations, with evidence of increasing severity of outcomes with increasing risk allele dosage. The clinical validity for the association of *9p21* polymorphisms with ischemic stroke, aneurysms, or other vascular disorders is less well-studied and less certain. Despite evidence that *9p21* polymorphisms are associated with CAD/CHD incidence and outcomes, the clinical utility of *9p21* genotyping has not been established. Studies have not conclusively demonstrated that *9p21* genotyping significantly improves risk reclassification after initial classification by traditional risk factors or that the addition of *9p21* genotyping to traditional risk factors improves risk assessment. No studies were identified that evaluate whether use of *9p21* genotyping is associated with changes in patient management,

improvements in clinical outcomes, or both. Thus, *9p21* genotyping for all applications is investigational.

Supplemental Information

American College of Cardiology and the American Heart Association

In 2013, the American College of Cardiology and the American Heart Association Task Force on Practice Guidelines issued guidelines on the assessment of cardiovascular risk, which did not address assessment of *9p21* polymorphisms.

Evaluation of Genomic Applications in Practice and Prevention Working Group

The Evaluation of Genomic Applications in Practice and Prevention Working Group (EWG) published a recommendation on "…genomic profiling to assess cardiovascular risk to improve cardiovascular health," which included a recommendation on 9p21 profiling alone based on Palomaki et al. In general, EWG found "…insufficient evidence to recommend testing for the 9p21 genetic variant or 57 other variants in 28 genes ... to assess risk for cardiovascular disease (CVD) in the general population, specifically heart disease and stroke. The EWG found that the magnitude of net health benefit from use of any of these tests alone or in combination is negligible. The EWG discourages clinical use unless further evidence supports improved clinical outcomes. Based on the available evidence, the overall certainty of net health benefit is deemed 'Low'."

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for *9p21* genotyping to identify risk for cardiovascular disease have been identified.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genotyping for 9p21 Single-Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm", 2.04.71, Archived March 2016.

2. Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. Jun 7 2007;447(7145):661-678. PMID 17554300
3. McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. Science. Jun 8 2007;316(5830):1488-1491. PMID 17478681
4. Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science. Jun 8 2007;316(5830):1491-1493. PMID 17478679
5. Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. N Engl J Med. Aug 2 2007;357(5):443-453. PMID 17634449
6. Scheffold T, Kullmann S, Huge A, et al. Six sequence variants on chromosome 9p21.3 are associated with a positive family history of myocardial infarction: a multicenter registry. BMC Cardiovasc Disord. 2011;11:9. PMID 21385355
7. Johansen CT, Lanktree MB, Hegele RA. Translating genomic analyses into improved management of coronary artery disease. Future Cardiol. Jul 2010;6(4):507-521. PMID 20608823
8. Harismendy O, Notani D, Song X, et al. 9p21 DNA variants associated with coronary artery disease impair interferon-gamma signalling response. Nature. Feb 10 2011;470(7333):264-268. PMID 21307941
9. Congrains A, Kamide K, Oguro R, et al. Genetic variants at the 9p21 locus contribute to atherosclerosis through modulation of ANRIL and CDKN2A/B. Atherosclerosis. Feb 2012;220(2):449-455. PMID 22178423
10. Kutyavin IV, Milesi D, Belousov Y, et al. A novel endonuclease IV post-PCR genotyping system. Nucleic Acids Res. 2006;34(19):e128. PMID 17012270
11. Palomaki GE, Melillo S, Bradley LA. Association between 9p21 genomic markers and heart disease: a meta-analysis. JAMA. Feb 17 2010;303(7):648-656. PMID 20159873
12. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. Genet Med. Jan 2009;11(1):3-14. PMID 18813139
13. Schunkert H, Konig IR, Kathiresan S, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat Genet. 2011;43(4):333-338. PMID 21378990
14. Preuss M, Konig IR, Thompson JR, et al. Design of the Coronary ARtery DIsease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Study: A Genome-wide association meta-

analysis involving more than 22 000 cases and 60 000 controls. Circ Cardiovasc Genet. Oct 1 2010;3(5):475-483. PMID 20923989
15. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. Nat Genet. 2011;43(4):339-344. PMID 21378988
16. Zhou LT, Qin L, Zheng DC, et al. Meta-analysis of genetic association of chromosome 9p21 with early-onset coronary artery disease. Gene. Dec 1 2012;510(2):185-188. PMID 22975211
17. Chan K, Patel RS, Newcombe P, et al. Association between the chromosome 9p21 locus and angiographic coronary artery disease burden: a collaborative meta-analysis. J Am Coll Cardiol. Mar 5 2013;61(9):957-970. PMID 23352782
18. Dong L, Wang H, Wang DW, et al. Association of chromosome 9p21 genetic variants with risk of coronary heart disease in the East Asian population: a meta-analysis. Ann Hum Genet. May 2013;77(3):183-190. PMID 23347249
19. Lian J, Ba Y, Dai D, et al. A replication study and a meta-analysis of the association between the CDKN2A rs1333049 polymorphism and coronary heart disease. J Atheroscler Thromb. 2014;21(11):1109-1120. PMID 24930384
20. Paynter NP, Chasman DI, Pare G, et al. Association between a literature-based genetic risk score and cardiovascular events in women. JAMA. Feb 17 2010;303(7):631-637. PMID 20159871
21. Ripatti S, Tikkanen E, Orho-Melander M, et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. Lancet. Oct 23 2010;376(9750):1393-1400. PMID 20971364
22. Dandona S, Stewart AF, Chen L, et al. Gene dosage of the common variant 9p21 predicts severity of coronary artery disease. J Am Coll Cardiol. Aug 3 2010;56(6):479-486. PMID 20670758
23. Patel RS, Su S, Neeland IJ, et al. The chromosome 9p21 risk locus is associated with angiographic severity and progression of coronary artery disease. Eur Heart J. Dec 2010;31(24):3017-3023. PMID 20729229
24. Davies RW, Dandona S, Stewart AF, et al. Improved prediction of cardiovascular disease based on a panel of single nucleotide polymorphisms identified through genome-wide association studies. Circ Cardiovasc Genet. Oct 1 2010;3(5):468-474. PMID 20729558
25. Beckie TM, Groer MW, Beckstead JW. The relationship between polymorphisms on chromosome 9p21 and age of onset of coronary heart disease in black and white women. Genet Test Mol Biomarkers. Jun 2011;15(6):435-442. PMID 21375403

26. Beckie TM, Beckstead JW, Groer MW. The association between variants on chromosome 9p21 and inflammatory biomarkers in ethnically diverse women with coronary heart disease: a pilot study. Biol Res Nurs. Jul 2011;13(3):306-319. PMID 21705410
27. Dutta A, Henley W, Lang IA, et al. The coronary artery disease-associated 9p21 variant and later life 20-year survival to cohort extinction. Circ Cardiovasc Genet. Oct 2011;4(5):542-548. PMID 21852414
28. Shiffman D, O'Meara ES, Rowland CM, et al. The contribution of a 9p21.3 variant, a KIF6 variant, and C-reactive protein to predicting risk of myocardial infarction in a prospective study. BMC Cardiovasc Disord. 2011;11:10. PMID 21406102
29. Wang W, Peng WH, Lu L, et al. Polymorphism on chromosome 9p21.3 contributes to early-onset and severity of coronary artery disease in non-diabetic and type 2 diabetic patients. Chin Med J (Engl). Jan 2011;124(1):66-71. PMID 21362310
30. Ardissino D, Berzuini C, Merlini PA, et al. Influence of 9p21.3 genetic variants on clinical and angiographic outcomes in early-onset myocardial infarction. J Am Coll Cardiol. Jul 19 2011;58(4):426-434. PMID 21757122
31. Szpakowicz A, Kiliszek M, Pepinski W, et al. Polymorphism of 9p21.3 locus is associated with 5-year survival in high-risk patients with myocardial infarction. PLoS One. 2014;9(8):e104635. PMID 25105296
32. Anderson CD, Biffi A, Rost NS, et al. Chromosome 9p21 in ischemic stroke: population structure and meta-analysis. Stroke. Jun 2010;41(6):1123-1131. PMID 20395606
33. Traylor M, Farrall M, Holliday EG, et al. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. Lancet Neurol. Nov 2012;11(11):951-962. PMID 23041239
34. Dichgans M, Malik R, Konig IR, et al. Shared genetic susceptibility to ischemic stroke and coronary artery disease: a genome-wide analysis of common variants. Stroke. Jan 2014;45(1):24-36. PMID 24262325
35. Ni X, Zhang J. Association between 9p21 genomic markers and ischemic stroke risk: evidence based on 21 studies. PLoS One. 2014;9(3):e90255. PMID 24625579
36. Chou SH, Shulman JM, Keenan BT, et al. Genetic susceptibility for ischemic infarction and arteriolosclerosis based on neuropathologic evaluations. Cerebrovasc Dis. 2013;36(3):181-188. PMID 24135527

37. Olsson S, Jood K, Blomstrand C, et al. Genetic variation on chromosome 9p21 shows association with the ischaemic stroke subtype large-vessel disease in a Swedish sample aged </= 70. Eur J Neurol. Feb 2011;18(2):365-367. PMID 20500804
38. Yue X, Tian L, Fan X, et al. Chromosome 9p21.3 Variants Are Associated with Cerebral Infarction in Chinese Population. J Mol Neurosci. Feb 11 2015. PMID 25665551
39. Alg VS, Sofat R, Houlden H, et al. Genetic risk factors for intracranial aneurysms: a meta-analysis in more than 116,000 individuals. Neurology. Jun 4 2013;80(23):2154-2165. PMID 23733552
40. Thompson AR, Golledge J, Cooper JA, et al. Sequence variant on 9p21 is associated with the presence of abdominal aortic aneurysm disease but does not have an impact on aneurysmal expansion. Eur J Hum Genet. Mar 2009;17(3):391-394. PMID 18854858
41. Helgadottir A, Thorleifsson G, Magnusson KP, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat Genet. Feb 2008;40(2):217-224. PMID 18176561
42. Bown MJ, Braund PS, Thompson J, et al. Association between the coronary artery disease risk locus on chromosome 9p21.3 and abdominal aortic aneurysm. Circ Cardiovasc Genet. Oct 2008;1(1):39-42. PMID 20031540
43. Biros E, Cooper M, Palmer LJ, et al. Association of an allele on chromosome 9 and abdominal aortic aneurysm. Atherosclerosis. Oct 2010;212(2):539-542. PMID 20605023
44. Wei Y, Xiong J, Zuo S, et al. Association of polymorphisms on chromosome 9p21.3 region with increased susceptibility of abdominal aortic aneurysm in a Chinese Han population. J Vasc Surg. Dec 20 2013. PMID 24365123
45. Lederle FA, Johnson GR, Wilson SE, et al. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. Arch Intern Med. May 22 2000;160(10):1425-1430. PMID 10826454
46. Wei Y, Xiong J, Zuo S, et al. Association of polymorphisms on chromosome 9p21.3 region with increased susceptibility of abdominal aortic aneurysm in a Chinese Han population. J Vasc Surg. Apr 2014;59(4):879-885. PMID 24365123
47. Murabito JM, White CC, Kavousi M, et al. Association between chromosome 9p21 variants and the ankle-brachial index identified by a meta-analysis of 21 genome-wide association studies. Circ Cardiovasc Genet. Feb 1 2012;5(1):100-112. PMID 22199011

48. O'Donnell CJ, Kavousi M, Smith AV, et al. Genome-wide association study for coronary artery calcification with follow-up in myocardial infarction. Circulation. Dec 20 2011;124(25):2855-2864. PMID 22144573
49. van Setten J, Isgum I, Smolonska J, et al. Genome-wide association study of coronary and aortic calcification implicates risk loci for coronary artery disease and myocardial infarction. Atherosclerosis. Jun 2013;228(2):400-405. PMID 23561647
50. Zhang X, Wen F, Zuo C, et al. Association of genetic variation on chromosome 9p21 with polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. Oct 2011;52(11):8063-8067. PMID 21896860
51. Cesana F, Nava S, Menni C, et al. Does the 9p region affect arterial stiffness? Results from a cohort of hypertensive individuals. Blood Press. Oct 2013;22(5):302-306. PMID 23445356
52. Sturiale CL, Fontanella MM, Gatto I, et al. Association between polymorphisms rs1333040 and rs7865618 of chromosome 9p21 and sporadic brain arteriovenous malformations. Cerebrovasc Dis. 2014;37(4):290-295. PMID 24820060
53. Bendjilali N, Nelson J, Weinsheimer S, et al. Common variants on 9p21.3 are associated with brain arteriovenous malformations with accompanying arterial aneurysms. J Neurol Neurosurg Psychiatry. Nov 2014;85(11):1280-1283. PMID 24777168
54. Folsom AR, Pankow JS, Li X, et al. No association of 9p21 with arterial elasticity and retinal microvascular findings. Atherosclerosis. Oct 2013;230(2):301-303. PMID 24075760
55. Paynter NP, Chasman DI, Buring JE, et al. Cardiovascular disease risk prediction with and without knowledge of genetic variation at chromosome 9p21.3. Ann Intern Med. Jan 20 2009;150(2):65-72. PMID 19153409
56. Talmud PJ, Cooper JA, Palmen J, et al. Chromosome 9p21.3 coronary heart disease locus genotype and prospective risk of CHD in healthy middle-aged men. Clin Chem. Mar 2008;54(3):467-474. PMID 18250146
57. Brautbar A, Ballantyne CM, Lawson K, et al. Impact of adding a single allele in the 9p21 locus to traditional risk factors on reclassification of coronary heart disease risk and implications for lipid-modifying therapy in the Atherosclerosis Risk in Communities study. Circ Cardiovasc Genet. Jun 2009;2(3):279-285. PMID 20031596
58. Sposito AC, Ramires JA, Jukema JW, et al. Physicians' attitudes and adherence to use of risk scores for primary prevention of cardiovascular disease: cross-sectional survey in three world regions. Curr Med Res Opin. May 2009;25(5):1171-1178. PMID 19323611

59. Sheridan SL, Crespo E. Does the routine use of global coronary heart disease risk scores translate into clinical benefits or harms? A systematic review of the literature. BMC Health Serv Res. 2008;8:60. PMID 18366711
60. Do R, Xie C, Zhang X, et al. The effect of chromosome 9p21 variants on cardiovascular disease may be modified by dietary intake: evidence from a case/control and a prospective study. PLoS Med. Oct 2011;8(10):e1001106. PMID 22022235
61. Gransbo K, Almgren P, Sjogren M, et al. Chromosome 9p21 genetic variation explains 13% of cardiovascular disease incidence but does not improve risk prediction. J Intern Med. Sep 2013;274(3):233-240. PMID 23480785
62. Downing KP, Nead KT, Kojima Y, et al. The combination of 9p21.3 genotype and biomarker profile improves a peripheral artery disease risk prediction model. Vasc Med. Feb 2014;19(1):3-8. PMID 24323119
63. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Jul 1 2014;63(25 Pt B):2935-2959. PMID 24239921
64. Recommendations from the EGAPP Working Group: genomic profiling to assess cardiovascular risk to improve cardiovascular health. Genet Med. Dec 2010;12(12):839-843. PMID 21042222

Policy History

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06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. New policy.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Title changed from "Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm" to "Genotyping for 9p21 Genetic Polymorphisms to Predict Cardiovascular Disease Risk". Coverage eligibility unchanged.
02/19/2013	Coding updated
06/06/2013	Medical Policy Committee review

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06/25/2013	Medical Policy Implementation Committee approval. Identification of patients at risk for aneurysmal disease added to the policy title and investigational statement, and additional cardiovascular disease added to policy statement (peripheral vascular disease, coronary artery calcification, polypoidal choroidal vasculopathy).
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2019	Medical Policy Committee review
06/19/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2022

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Coding

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

Code Type	Code
CPT	81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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.

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