Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

Policy # 00382
Original Effective Date: 09/18/2013
Current Effective Date: 01/01/2023

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: Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) is addressed separately in medical policy 00047.

Note: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes is addressed separately in medical policy 00190.

Note: Genetic Testing for Li-Fraumeni Syndrome is addressed separately in medical policy 00424.

Note: Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1) is addressed separately in medical policy 00504.

Note: Use of Common Genetic Variants (single nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer is addressed separately in medical policy 00268.

Note: Genetic Testing for PTEN Hamartoma Tumor Syndrome is addressed separately in medical policy 00417.

Note: Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes is addressed separately in medical policy 00706.

Note: Genetic Testing for Familial Cutaneous Malignant Melanoma is addressed separately in medical policy 00206.
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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 general genetic cancer susceptibility panel testing to be investigational;* however, when the coverage criteria of other policies are met (see related policies above), then limited genetic cancer susceptibility panels including only the gene variants for which a given member qualifies may be considered to be eligible for coverage.**

Policy Guidelines
Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
</tbody>
</table>
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| Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling
Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview
Genetic Testing for Cancer Susceptibility
Genetic testing for cancer susceptibility may be approached by a focused method that involves testing for gene(s) that may be the cause of the heritable or familial cancer. Panel testing with next-generation sequencing (NGS) involves evaluating sequence variants in multiple genes at one time.
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Multiple commercial companies and medical center laboratories offer genetic testing panels that use NGS methods for hereditary cancers. Next-generation sequencing is one of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic variants of uncertain clinical significance or findings that would not lead to changes in patient management.

Genes Included in Next-Generation Sequencing Panels
The following summarizes the function and disease association of major genes included in NGS panels. This summary is not comprehensive.

**BRCA1 and BRCA2 Variants**
BRCA1 and BRCA2 germline variants are associated with hereditary breast and ovarian cancer syndrome, which is associated most strongly with increased susceptibility to breast cancer at an early age, bilateral breast cancer, male breast cancer, ovarian cancer, cancer of the fallopian tube, and primary peritoneal cancer. BRCA1 and BRCA2 variants are also associated with increased risk of other cancers, including prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

**APC Variants**
APC germline variants are associated with familial adenomatous polyposis (FAP) and attenuated FAP. Familial adenomatous polyposis is an autosomal dominant colon cancer predisposition syndrome characterized by hundreds to thousands of colorectal adenomatous polyps and accounts for about 1% of all colorectal cancers (CRCs).

**ATM Variants**
ATM is associated with the autosomal recessive condition ataxia-telangiectasia. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition, particularly leukemia and lymphoma.

**BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C Variants**
BARD1, BRIP1, MRE11A, NBN, RAD50, and RAD51C are genes in the Fanconi anemia/BRCA pathway. Variants in these genes are estimated to confer up to a 4-fold increase in the risk of breast
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cancer. This pathway is also associated with a higher risk of ovarian cancer and, less often, pancreatic cancer.

**BMPR1A and SMAD4 Variants**

*BMPR1A* and *SMAD4* are genes mutated in juvenile polyposis syndrome and account for 45% to 60% of cases. Juvenile polyposis syndrome is an autosomal dominant disorder that predisposes to the development of polyps in the gastrointestinal tract. Malignant transformation can occur, and the risk of gastrointestinal cancer has been estimated from 9% to 50%.

**CHEK2 Variants**

*CHEK2* gene variants confer an increased risk of developing several different types of cancer, including breast, prostate, colon, thyroid, and kidney. *CHEK2* regulates the function of the BRCA1 protein in DNA repair and has been associated with familial breast cancers.

**CDH1 Variants**

*CDH1* is a tumor suppressing gene located on chromosome 16q22.1 that encodes the cell-to-cell adhesion protein E-cadherin. Germline variants in the *CDH1* gene have been associated with an increased risk of developing hereditary diffuse gastric cancer (DGC) and lobular breast cancer. A diagnosis of HDGC can be confirmed by genetic testing, although 20% to 40% of families with suspected HDGC do not have a *CDH1* variant on genetic testing. Pathogenic *CDH1* variants have been described in Maori families in New Zealand, and individuals of Maori ethnicity have a higher prevalence of diffuse-type gastric cancer than non-Maori New Zealanders. *CDH1* germline variants are associated with lobular breast cancer in women and with hereditary diffuse gastric cancer (DGC). The estimated cumulative risk of gastric cancer for *CDH1* variant carriers by age 80 years is 70% for men and 56% for women. *CDH1* variants are associated with a lifetime risk of 39% to 52% of lobular breast cancer.

**EPCAM, MLH1, MSH2, MSH6, and PMS2 Variants**

*EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* are mismatch repair genes associated with Lynch syndrome (hereditary nonpolyposis CRC). Lynch syndrome is estimated to cause 2% to 5% of all colon cancers. Lynch syndrome is associated with a significantly increased risk of several types of cancer-colon cancer (60% to 80% lifetime risk), uterine/endometrial cancer (20% to 60% lifetime risk), gastric cancer (11% to 19% lifetime risk), and ovarian cancer (4% to 13% lifetime risk). The
risks of other types of cancer, including the small intestine, hepatobiliary tract, upper urinary tract, and brain, are also elevated.

**MUTYH Variants**
*MUTYH* germline variants are associated with an autosomal recessive form of hereditary polyposis. It has been reported that 33% and 57% of patients with clinical FAP and attenuated FAP, respectively, who are negative for variants in the *APC* gene, have *MUTYH* variants.

**PALB2 Variants**
*PALB2* germline variants are associated with an increased risk of pancreatic and breast cancer. Familial pancreatic and/or breast cancer due to *PALB2* variants are inherited in an autosomal dominant pattern.

**PTEN Variants**
*PTEN* variants are associated with *PTEN* hamartoma tumor syndrome (PHTS), which includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome. Cowden syndrome is characterized by a high risk of developing tumors of the thyroid, breast, and endometrium. Affected persons have a lifetime risk of up to 50% for breast cancer, 10% for thyroid cancer, and 5% to 10% for endometrial cancer.

**STK11 Variants**
*STK11* germline variants are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, with a 57% to 81% risk of developing cancer by age 70, of which gastrointestinal and breast cancers are the most common.

**TP53 Variants**
*TP53* variants are associated with Li-Fraumeni syndrome. People with *TP53* variants have a 50% risk of developing any of the associated cancers by age 30 and a lifetime risk up to 90%, including sarcomas, breast cancer, brain tumors, and adrenal gland cancers.

**NF1 Variants**
The *NF1* gene encodes a negative regulator in the *ras* signal transduction pathway. Variants in the *NF1* gene have been associated with neurofibromatosis type 1, juvenile myelomonocytic leukemia, malignant peripheral nerve sheath tumor, brain cancer, breast cancer, and Watson syndrome.
RAD51D Variants
RAD51D germline variants are associated with familial breast and ovarian cancers.

CDK4 Variants
Cyclin-dependent kinase-4 is a protein-serine kinase involved in cell cycle regulation. Variants in the CDK4 gene are associated with a variety of cancers, particularly cutaneous melanoma.

CDKN2A Variants
The CDKN2A gene encodes proteins that act as multiple tumor suppressors through their involvement in 2 cell cycle regulatory pathways: the p53 pathway and the RB1 pathway. Variants or deletions in CDKN2A are frequently found in multiple types of tumor cells. Germline variants in CDKN2A have been associated with the risk of melanoma, along with pancreatic and central nervous system cancers.

RET Variants
RET encodes a receptor tyrosine kinase; variants in this gene are associated with multiple endocrine neoplasia syndromes (types IIA and IIB) and medullary thyroid carcinoma.

SDHA, SDHB, SDHC, SDHD, and SDHAF2 Variants
SDHA, SDHB, SDHC, SDHD, and SDHAF2 gene products are involved in the assembly and function of a component of the mitochondrial respiratory chain. Germline variants in these genes are associated with the development of paragangliomas, pheochromocytomas, gastrointestinal stromal tumors, and a PTEN-negative Cowden-like syndrome.

TMEM127 Variants
TMEM127 germline variants are associated with the risk of pheochromocytomas.

VHL Variants
VHL germline variants are associated with Hippel-Lindau syndrome, an autosomal dominant familial cancer syndrome. This syndrome is associated with various malignant and benign tumors, including central nervous system tumors, renal cancers, pheochromocytomas, and pancreatic neuroendocrine tumors.
FH Variants
FH variants are associated with renal cell and uterine cancers.

FLCN Variants
FLCN acts as a tumor suppressor gene; variants in this gene are associated with the autosomal dominant Birt-Hogg-Dube syndrome, which is characterized by hair follicle hamartomas, kidney tumors, and CRC.

MET Variants
MET is a proto-oncogene that acts as the hepatocyte growth factor receptor. MET variants are associated with hepatocellular carcinoma and papillary renal cell carcinoma.

MITF Variants
Microphthalmia-associated transcription factor (encoded by the MITF gene) is a transcription factor involved in melanocyte differentiation. MITF variants lead to several auditory-pigmentary syndromes, including Waardenburg syndrome type 2 and Tietze syndrome. MITF variants are also associated with melanoma and renal cell carcinoma.

TSC1 Variants
TSC1 and TSC2 encode the proteins hamartin and tuberin, which are involved in cell growth, differentiation, and proliferation. Variants in these genes are associated with the development of tuberous sclerosis complex, an autosomal dominant syndrome characterized by skin abnormalities, developmental delay, seizures, and multiple types of cancers, including central nervous system tumors, renal tumors (including angiomyolipomas, renal cell carcinomas), and cardiac rhabdomyomas.

XRCC2 Variants
XRCC2 encodes proteins thought to be related to the RAD51 protein product that is involved in DNA double-stranded breaks. Variants may be associated with Fanconi anemia and breast cancer.

FANCC Variants
FANCC is one of several DNA repair genes that mutate in Fanconi anemia, which is characterized by bone marrow failure and a high predisposition to multiple types of cancer.
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AXIN2 Variants
AXIN2 variants are associated with FAP syndrome, although the phenotypes associated with AXIN2 variants do not appear to be well-characterized.

Hereditary Cancer and Cancer Syndromes
Genetic testing for breast and ovarian cancer syndromes is evaluated in separate policies.

Genetic testing for Li-Fraumeni syndrome is evaluated in a separate policy.

Cowden syndrome is a part of PHTS and is the only PHTS disorder associated with a documented predisposition to malignancies. Genetic testing for CS is a separate policy.

Genetic testing for hereditary colon cancer syndromes is addressed in a separate policy.

Genetic testing for familial pancreatic testing is evaluated in a separate policy.

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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of these tests.

Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Commercially available cancer susceptibility gene panels can test for multiple variants associated with a specific type of cancer or can include variants associated with a wide variety of cancers.
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of these variants are associated with inherited cancer syndromes. The cancer type(s), as well as a cancer history involving multiple family members, increase the clinical concern for the presence of a heritable genetic variant. It has been proposed that variant testing using next-generation sequencing (NGS) technology to analyze multiple genes at one time (panel testing) can optimize genetic testing in these patients compared with sequencing single genes.

There is limited evidence on clinical validity for many of the genes in expanded panels. Most studies have been retrospective. These studies have reported on the frequency with which well-known cancer susceptibility variants are identified using large panels and variably have reported the VUS rate. The VUS rates increased in proportion with panel size, reaching nearly 50% for large gene panels. Although it may be possible to evaluate the clinical validity of some of the genes found on these panels, the clinical validity of expanded cancer susceptibility panels, which include variants associated with unknown or variable cancer risk, are of uncertain clinical validity.

Data are lacking for the clinical utility of multi-gene panels for inherited cancer susceptibility panels. There are management guidelines for syndromes with high penetrance, which have clinical utility in that they inform clinical decision making and result in the prevention of adverse health outcomes. Clinical management recommendations for the inherited conditions associated with low-to-moderate penetrance are not standardized, and the clinical utility of genetic testing for these variants is uncertain and could potentially lead to harm. Also, high VUS rates have been reported with the use of these panels.

Summary of Evidence
For individuals who have a personal and/or family history suggesting an inherited cancer syndrome who receive expanded gene panel testing, the evidence includes reports describing the diagnostic yield of expanded gene panels. Relevant outcomes are overall survival, disease-specific survival, and test validity. Studies of gene panel testing for genetic cancer risk assessment have reported primarily on the frequency with which variants are identified. The rates of variants of uncertain significance for gene panels are significant and increase in proportion with panel size, reaching nearly 50% for large gene panels. Variants included in these panels are associated with varying levels of risk of developing cancer. Published data on clinical utility are lacking, and it is unknown whether the use of these panels improves health outcomes. Only some variants included on panels are associated with a high risk of developing a well-defined cancer syndrome for which there are established clinical management guidelines. Many expanded panels include genetic variants...
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considered to be of moderate or low penetrance, and clinical management recommendations for these genes are not well-defined. The lack of clinical management pathways for variants of uncertain clinical significance increases the potential for harm. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Supplemental Information**
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

**Practice Guidelines and Position Statements**
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

**American Society of Clinical Oncology**
In 2015, the American Society of Clinical Oncology (ASCO) issued a policy statement on genetic and genomic testing for cancer susceptibility. The update addressed the application of next-generation sequencing (NGS) and confirmed that panel testing may also identify variants in genes associated with moderate or low cancer risks, variants in high-penetrance genes that would not have been evaluated based on the presenting personal or family history, and variants of uncertain significance in a substantial proportion of patient cases. Further, the statement indicated there is little consensus as to which genes should be included on panels for cancer susceptibility testing.

In 2020, ASCO published a guideline on germline and somatic tumor testing in epithelial ovarian cancer. Based on a systematic review of evidence and expert panel input, ASCO recommended that women with epithelial ovarian cancer should be offered germline testing for *BRCA1/2* and other specified ovarian susceptibility genes with a multi-gene panel. It was considered more practical to evaluate a minimum of the 10 genes that have been associated with inherited risk of ovarian cancer in a panel in comparison to testing *BRCA1* and *BRCA2* alone.
National Comprehensive Cancer Network

Breast and Ovarian Cancers

National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast, ovarian cancers, and/or pancreatic cancer (v.2.2022) include the following on multi-gene testing:

- "An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a tailored multi-gene panel test is often more efficient and cost-effective and increases the yield of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or their at-risk family members.

- There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.

- Some individuals may carry a pathogenic/likely pathogenic germline variants in more than one cancer susceptibility gene..."

The NCCN defines a "tailored" multi-gene panel test as a "disease-focused multi-gene panel of clinically actionable cancer susceptibility genes, in contrast to large multi-gene panels of uncertain or unknown clinical relevance." The NCCN cautions that multi-gene panels may include moderate-risk genes that have limited data on the degree of cancer risk and no clear guidelines on risk management. As more genes are testing, the likelihood of finding variants of uncertain significance increases. Multi-gene panel testing also increases the likelihood of finding pathogenic/likely pathogenic variants without clear significance.

Colorectal Cancer

The NCCN guidelines on genetic/familial high-risk assessment for colorectal cancer (v.1.2022) state that "when more than one gene can explain an inherited cancer syndrome, multi-gene testing is more efficient than single-gene testing, or sequential single syndrome testing" and "there is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility." However, the NCCN cautioned about the increased likelihood of finding variants of uncertain significance, which increases with the number of genes included in the panel, and that gene panels can include moderate-risk genes that may not be clinically actionable.
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Collaborative Group of the Americas on Inherited Gastrointestinal Cancer
In 2020, the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer published a position statement on multi-gene panel testing for patients with colorectal cancer and/or polyposis. Recommendations were based on the evidence, professional society recommendations endorsing testing of a given gene, and opinion of the expert panel. The group noted the variability in genes included in commercially available panels and recommended that multi-gene panels include a minimum of 11 specific genes associated with defective mismatch repair (Lynch syndrome) and polyposis syndromes. Additional genes to be considered had low to moderately increased risk, had limited data of colorectal cancer risk, or causation for colorectal cancer was not proven.

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force (2019) has recommended that primary care providers screen women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutations with an appropriate brief familial risk assessment tool. Women with positive screening results should receive genetic counseling and if indicated after counseling, BRCA testing (grade B recommendation). The use of genetic cancer susceptibility panels was not specifically mentioned.

Medicare National Coverage
In January 2020, the Centers for Medicare and Medicaid Services (CMS) determined that NGS is covered for patients with breast or ovarian cancer when the diagnostic test is performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory AND the test has approval or clearance by the U.S. FDA (CAG-00450R).

CMS states that local Medicare carriers may determine coverage of NGS for management of the patient for any cancer diagnosis with a clinical indication and risk factor for germline testing of hereditary cancers when performed in a CLIA-certified laboratory.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.
Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
</table>

NCT: national clinical trial.

References

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Policy History

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09/05/2013    Medical Policy Committee review
09/18/2013    Medical Policy Implementation Committee approval. New policy.
09/04/2014    Medical Policy Committee review
09/17/2014    Medical Policy Implementation Committee approval. No change to coverage.
01/01/2015    Coding Update
09/03/2015    Medical Policy Committee review
09/23/2015    Medical Policy Implementation Committee approval. No change to coverage.
09/08/2016    Medical Policy Committee review
09/21/2016    Medical Policy Implementation Committee approval. No change to coverage.
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. No change to coverage.
12/06/2018    Medical Policy Committee review
12/19/2018    Medical Policy Implementation Committee approval. No change to coverage. Added policy guidelines.
06/17/2019    Coding update
12/05/2019    Medical Policy Committee review
12/11/2019    Medical Policy Implementation Committee approval. No change to coverage. Coding update
12/03/2020    Medical Policy Committee review
12/09/2020    Medical Policy Implementation Committee approval. No change to coverage.
12/02/2021    Medical Policy Committee review

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12/08/2021 Medical Policy Implementation Committee approval. Investigational statement reworded.
03/08/2022 Coding Update
03/25/2022 Coding Update
04/13/2022 Coding Update
12/01/2022 Medical Policy Committee review
12/14/2022 Medical Policy Implementation Committee approval. No change to coverage. Senate bill review.

Next Scheduled Review Date: 12/2023

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 2021 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.

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

<table>
<thead>
<tr>
<th>Code Type</th>
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| CPT       | 81437, 81438, 81479  
Delete code effective 5/1/2022: 0012M  
Add code effective 01/01/2023: 81442  
Delete codes effective 01/01/2023: 0049U, 81162, 81163, 81164, 81165, 81166, 81167, 81201, 81202, 81203, 81206, 81207, 81208, 81210, 81212, 81215, 81216, 81217, 81235, 81270, 81275, 81276, 81287, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81309, 81317, 81318, 81319, 81321, 81322, 81323, 81345, 81432, 81433, 81443, 81445 |
| 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 technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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3. Reference to federal regulations.

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NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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.