Mutation Analysis in Myeloproliferative Neoplasms AHS - M2101

Description of Procedure or Service

Myeloproliferative neoplasms (MPN) are a heterogeneous group of clonal disorders characterized by overproduction of one or more differentiated myeloid lineages (Grinfeld, Nangalia, & Green, 2017). These include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The majority of MPN result from somatic mutations in the 3 driver genes, \textit{JAK2}, \textit{CALR}, and \textit{MPL}, which represent major diagnostic criteria in combination with hematologic and morphological abnormalities (Rumi & Cazzola, 2017).

Myeloproliferative neoplasms arise from somatic mutation in hematopoietic stem cell (HSC) that clonally expand resulting in single or multilineage hyperplasia (Vainchenker & Kralovics, 2017). They are relatively rare affecting 0.84 (PV), 1.03 (ET), and 0.47(PMF) people per 100,000 worldwide (Titmarsh et al., 2014), however these may not be reflective of its true incidence due to the high heterogeneity of MPN.

Related Policies:
BCR-ABL 1 Testing for Chronic Myeloid Leukemia

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Mutation Analysis in Myeloproliferative Neoplasms when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Mutation Analysis in Myeloproliferative Neoplasms is covered

1. \textit{JAK2}, \textit{CALR} or \textit{MPL} mutation testing is considered medically necessary for the diagnosis of patients presenting with clinical, laboratory, or pathological findings suggesting classic forms of myeloproliferative neoplasms (MPN), that is, polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) when ordered by a hematology and/or oncology specialist in the following situations:
Mutation Analysis in Myeloproliferative Neoplasms AHS - M2101

A. Patients suspected to have polycythemia vera (PV) should first be tested for the most common finding JAK2V617F.
   i. If testing is negative, further testing to detect other JAK2 tyrosine kinase mutations, eg, in exon 12, is considered medically necessary.
   
   ii. For patients suspected to have PV, JAK2 mutation testing is considered medically necessary only if one of the following testing criteria are met:
   1. Hemoglobin >16.5 g/dL in men; Hemoglobin >16.0 g/dL in women, or
   Hematocrit >49% in men; Hematocrit >48% in women, on two separate occasions or
   Increased red cell mass (More than 25% above mean normal predicted value), and no other known cause of erythrocytosis, or
   2. Bone marrow biopsy showing hypercellularity for age with trilineage hyperplasia including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

B. For patients suspected to have essential thrombocythemia (ET) testing for JAK2, CALR and MPL mutations is considered medically necessary only if one of the following testing criteria are met:
   1. Platelet count ≥450 × 10^9/L greater than 3 months or
   2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers.

C. For patients suspected to have primary myelofibrosis (PMF), testing for JAK2, CALR and MPL mutations is considered medically necessary if any the following testing criteria are met:
   1. Patient has demonstrated leukocytosis of greater or equal to 11 x 10^9 (9) on two separate occasions in the absence of other conditions that can cause leukocytosis or
   2. Enlarged spleen or
   3. BM biopsy shows megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis or
   4. BM biopsy shows presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3

2. JAK2 mutation testing is considered medically necessary in individuals diagnosed with Budd-Chiari Syndrome.

NOTE: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.

When Mutation Analysis in Myeloproliferative Neoplasms is not covered

JAK2 tyrosine kinase, CALR, and MPL mutation testing is considered investigational in all other cases.

Policy Guidelines
Mutation Analysis in Myeloproliferative Neoplasms AHS - M2101

Scientific Background

Myeloproliferative neoplasms, including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), arise from somatic mutation in hematopoietic stem cell (HSC) that clonally expand resulting in single or multilineage hyperplasia (Vainchenker & Kralovics, 2017). They are relatively rare, affecting 0.84 (PV), 1.03 (ET), and 0.47 (PMF) people per 100,000 worldwide; however, these may not be reflective of its true incidence due to the high heterogeneity of MPN (Titmarsh et al., 2014).

MPNs share features of bone marrow hypercellularity, increased incidence of thrombosis or hemorrhage, and an increased rate of progression to acute myeloid leukemia. Abnormalities in cytokine signaling pathways are common and usually lead to increased JAK-STAT signaling (Grinfeld et al., 2017). PV is characterized by erythrocytosis with suppressed endogenous erythropoietin production, bone marrow panmyelosis, and JAK2 mutation leading to constitutive activation. ET is defined by thrombocytosis, bone marrow megakaryocytic proliferation, and presence of JAK2, CALR, or MPL mutation. PMF is characterized by bone marrow megakaryocytic proliferation, reticulin and/or collagen fibrosis, and presence of JAK2, CALR, or MPL mutation (Rumi & Cazzola, 2017). Mutations in other genes involved in signal transduction (CBL, LNK/SH2B3), chromatin modification (TET2, EZH2, IDH1/2, ASXL1, DNM3TA), RNA splicing (SF3B1, SRSF2, U2AF1), and tumor suppressor function (TP53) have also been reported and are considered “high-risk” (NCCN, 2019).

JAK2, which stands for “Janus Kinase 2”, is a gene whose mutation is responsible for a significant amount of MPNs. It is a mutation that causes hypersensitivity of hematopoietic progenitor cells to other cytokines, and this mutation typically appears on red blood cells or bone marrow cells. This mutation is often found on exon 12 or 14, and the exon 14 mutation results in a cytokine-independent activation of several regulatory pathways. JAK2 mutations contribute to at least 95% of PV cases, about 50-65% of ET cases, and 60-65% of PMF cases (Ayalew Tefferi, 2018a, 2018b, 2018c).

MPL, which encodes a thrombopoietin receptor, also contributes to MPNs. MPL mutations result in a similar phenotype to JAK2 mutations; both result in cytokine-independent growth of their targets. However, MPL mutations are not nearly as common as JAK2 and CALR mutations, casting doubt on the clinical utility for testing. MPL mutations comprise up to 4% of ET cases and 5% of PMF cases (Ayalew Tefferi, 2018a, 2018b, 2018c).

CALR is a gene that encodes calreticulin (or calregulin), which is a Ca2+ binding protein. The mutation typically involves the creation of the incorrect Ca2+ binding region, thereby not allowing the protein to perform its regular duties such as maintaining calcium homeostasis. This results in a similar phenotype to the JAK2 mutation, which is the cytokine-independent activation of regulatory pathways. CALR mutations contribute to approximately 15-25% of ET cases and 20-25% of PMF cases, and about 70% of ET or PMF patients without a JAK2 or MPL mutation have this mutation (Ayalew Tefferi, 2018a, 2018b, 2018c).

The significance of JAK2, MPL, CALR and other mutations in the genesis of the MPNs as well as their roles in determining phenotype are unclear (Ayalew Tefferi, 2019). However, integrated genomic analyses suggest that regardless of diagnosis or JAK2 mutational status, MPNs are characterized by upregulation of JAK-STAT target genes, demonstrating the central importance of this pathway in the pathogenesis (Rampal et al., 2014). This may lead to development of novel JAK2 therapeutics (Silvennoinen & Hubbard, 2015). Thus, mutation analysis at the time of diagnosis has value for determining prognosis as well as individual risk assessment and guide treatment-making decisions (Hussein, Granot, Shpilberg, & Kreipe, 2013; Ayalew Tefferi, 2018d).

In 2017 the FDA approved ipsogen® JAK2 RGQ PCR Kit (FDA, 2017b) to detect Janus Tyrosine Kinase 2 (JAK2) gene mutation G1849T (V617F) with an allele-specific, quantitative, polymerase chain reaction (PCR) using an amplification refractory mutation system (ARMS). The device marketing authorization was based on data from a clinical study of 473 suspected patients with MPNs, 276 with suspected PV, 98 with suspected ET, and 99 with suspected PMF. The study compared results from the ipsogen JAK2 RGQ
PCR Kit to results obtained with independently validated bi-directional sequencing. The study found that the ipsogen JAK2 RGQ PCR Kit test was in 96.8% agreement with the reference method, 100% in positive agreement, and 95.1% in negative agreement, with 458 samples in agreement out of 473. The concordance with each condition was also high; agreement of 90.8% within the ET samples (89/98), 94.9% agreement within the PMF samples (94/99), and 99.6% within the PV samples (275/276). All three conditions had positive agreements of 100%. The authors went on to note that the 15 samples with disagreeing results had mutation levels under the detection capability of bi-directional sequencing. To validate these 15 samples, an independently validated NGS panel was used to compare results with the kit, and all 15 samples were found to test positive, thereby agreeing with the kit. The authors concluded that the kit was accurate for any mutation levels at or above 1% (FDA, 2017a).

Genoptix, Inc. offers multiple testing options for JAK2 testing. One option is a myeloid molecular profile test of genomic DNA from either bone marrow aspirates or blood. These test uses NGS technology to sequence 44 different genes, including JAK2, CLR, MPL, SETBP1, and CSF3R in addition to KRAS, NRAS, and other genes. Genoptix claims to identify at least one somatic mutation in 80 – 90% of patients with a myelodysplastic syndrome, including MPN (Genoptix, 2018b). Genoptix also offers a test titled “MPN Targeted Profile”, an NGS test focused on targeted regions of JAK2, CALR, MPL, CSF3R, and SETBP1. They note that “the MPN Molecular Profile is intended as an aid in the diagnosis and subclassification of BCR-ABL1-negative myeloproliferative neoplasms (MPN) (Genoptix, 2018a).” CSF3R mutations have been discovered in a majority of patients with chronic neutrophilic leukemia (CNL) (A. Tefferi, Thiele, Vannucchi, & Barbi, 2014). A study released in 2013 reported 16 of 27 patients with CNL or atypical chronic myeloid leukemia (aCML) had activating mutations in CSF3R (Maxson et al., 2013). SETBP1 has been used as a part of comprehensive mutation profiling in distinguishing aCML and chronic myelomonocytic leukemia (CMML). A 2019 NGS study reports significant differences in the profiles of patients with aCML or CMML when comparing TET2, SETBP1, and CSF3R. The researchers conclude, “differential mRNA expression could be detected between both cohorts in a subset of genes (FLT3, CSF3R, and SETBP1 showed the strongest correlation). However, due to high variances in the mRNA expression, the potential utility for the clinic is limited (Faisal et al., 2019).”

Guidelines and Recommendations

**World Health Organization**

The 2017 edition of the World Health Organization’s classification of myeloid neoplasm and acute leukemia proposed the following criteria for the diagnosis of PV, ET and PMF.

**WHO Criteria for PV**

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion:

**Major Criteria**
1. Hemoglobin >16.5 g/dL in men; Hemoglobin >16.0 g/dL in women, or Hematocrit >49% in men; Hematocrit >48% in women, or Increased red cell mass (More than 25% above mean normal predicted value)
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of \( JAK2V617F \) or \( JAK2 \) exon 12 mutation

**Minor Criteria**
- Subnormal serum erythropoietin level

**WHO Criteria for ET**

Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion:

**Major Criteria**
1. Platelet count ≥450 × 10⁹/L
An Independent Licensee of the Blue Cross and Blue Shield Association

Mutation Analysis in Myeloproliferative Neoplasms AHS - M2101

2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers

3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms

4. Presence of JAK2, CALR, or MPL mutation

Minor Criteria
- Presence of a clonal marker or absence of evidence for reactive thrombocytosis

WHO Criteria for PrePMF

Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion:

Major Criteria
- Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
- Not meeting the WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms
- Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker (e.g. ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1), or absence of minor reactive BM reticulin fibrosis

Minor Criteria
- Anemia not attributed to a comorbid condition
- Leukocytosis ≥11 × 10⁹/L
- Palpable splenomegaly
- LDH increased to above upper normal limit of institutional reference range

WHO Criteria for Overt PMF

Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion:

Major Criteria
- Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
- Not meeting WHO criteria for ET, PV, BCR-ABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasms
- Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker (e.g. ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1), or absence of reactive myelofibrosis

Minor Criteria
- Anemia not attributed to a comorbid condition
- Leukocytosis ≥11 × 10⁹/L
- Palpable splenomegaly
- LDH increased to above upper normal limit of institutional reference range
- Leukoerythroblastosis (T. Barbui et al., 2018)

These guidelines also list four additional “clinicopathologic entities” for MPNs: “chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, not otherwise specified (CELNOS) and MPN, unclassifiable (MPN-U)”. The guidelines note that although CSF3R mutations are “specific” to WHO-defined CNL, they also remark that “the presence of a membrane proximal CSF3R mutation in a patient with neutrophilic granulocytosis should be sufficient for the diagnosis of CNL, regardless of the degree of leukocytosis” (T. Barbui et al., 2018).

European LeukemiaNet (ELN)

ELN guidelines also recommend “strict adherence” to these guidelines for the three categories of Philadelphia-negative MPNs, (i.e. ET, PV, and MF) (Tiziano Barbui et al., 2018).
Mutation Analysis in Myeloproliferative Neoplasms AHS - M2101

However, they also recommend “searching” for complementary clonal markers such as \textit{ASXL1}, \textit{EZH2}, \textit{IDH1/2}, and \textit{SRSF2} for patients that tested negative for the three driver mutations and have bone marrow features as well as a clinical phenotype consistent with myelofibrosis (Tiziano Barbui et al., 2018).

\textbf{National Comprehensive Cancer Network (NCCN, 2019)}

The NCCN Guidelines Version 3.2019 for Myeloproliferative Neoplasms recommends “molecular testing for JAK2 V617F mutations as part of an initial workup for all patients molecular testing for CALR and MPL mutations should be performed for ET and PMF patients, and molecular testing for JAK2 exon 12 should be done for patients who test negative for JAK2 but are suspected for PV. An NGS panel including JAK2, CALR, and MPL may also be used. The NCCN follows the 2017 edition of the WHO diagnostic criteria for all three conditions. The NCCN does state that NGS “may be useful to establish clonality in selected circumstances (eg, triple negative non-mutated JAK2, MPL, and CALR). They include a list of somatic mutations with prognostic significance in individuals with MPN that includes the \textit{ASXL1}, \textit{EZH2}, \textit{IDH1/2}, \textit{SRSF2}, \textit{TP53}, and \textit{U2AF1 Q157}.

\textbf{British Society for Haematology (BSH, 2014)}

The BSH recommends testing for CALR for patients suspected of ET and PMR, as CALR mutations account for most patients without either a JAK2 or MPL mutation. The authors found that as many as one third of ET and PMF patients had a mutation in exon 9 of the CALR gene (Harrison et al., 2014).

The BSH also published guidelines on the diagnosis of polycythaemia vera (PV). In it, they divide PV into JAK2-positive and JAK2-negative PV. For \textit{JAK2}-positive PV, the only two diagnostic criteria are as follows:

- “High haematocrit (>0·52 in men, >0·48 in women) OR raised red cell mass (>25% above predicted)”
- “Mutation in \textit{JAK2}”

For \textit{JAK2}-negative PV, the diagnostic criteria are as follows (requiring A1-A4, as well as another “A” criteria or two “B” criteria).

- “A1 Raised red cell mass (>25% above predicted) OR haematocrit ≥0·60 in men, ≥0·56 in women”
- “A2 Absence of mutation in \textit{JAK2}”
- “A3 No cause of secondary erythrocytosis”
- “A4 Bone marrow histology consistent with polycythaemia vera”
- “A5 Palpable splenomegaly”
- “A6 Presence of an acquired genetic abnormality (excluding BCR-ABL1) in the haematopoietic cells”
- “B1 Thrombocytosis (platelet count >450 \times 10^9 /l)”
- “B2 Neutrophil leucocytosis (neutrophil count >10 \times 10^9 /l in non-smokers, ≥12.5 \times 10^9 /l in smokers)”
- “B3 Radiological evidence of splenomegaly”
- “B4 Low serum erythropoietin”

The guidelines also note that investigation of erythrocytosis should be undertaken to properly identify the diagnosis. The BSH remarks that EPO receptor mutations may be a primary cause for erythrocytosis and
Mutation Analysis in Myeloproliferative Neoplasms AHS - M2101

that EGNLI, VHL, and EPAS1 mutations may be a secondary cause. Other hemoglobinopathies caused by mutations in genes such as HBA1, HBA2, HBB, or BGPM may also be a factor (McMullin et al., 2019).

European Association for the Study of the Liver (EASL, 2015)

For myeloproliferative neoplasms, the EASL recommends testing for JAK2 V617F mutations in splanchnic vein thrombosis patients, as well as patients with normal peripheral blood cell counts. If the JAK2 mutation test is negative, a calreticulin mutation test should be performed, and if both are negative, a bone marrow histology analysis should be performed (EASL, 2016).

European Society of Medical Oncology (ESMO, 2015)

The ESMO recommends that anyone with a suspected MPN be tested for the three driver mutations (JAK2, CALR, MPL) and that genotyping should be obtained at diagnosis. However, the ESMO states that it is not recommended to repeat testing in follow-up or assessing response to treatment, except for “allogeneic stem-cell transplantation and possibly interferon treatment”. For these two assessments a detection limit of ≤1% is recommended. The ESMO also notes that conventional sequencing methods (PCR, melting analysis) may be used for detecting mutations (Vannucchi et al., 2015).

State and Federal Regulations, as applicable

On July 28, 2017 the FDA approved ipsogen® JAK2 RGQ PCR Kit (FDA, 2017b) to detect Janus Tyrosine Kinase 2 (JAK2) gene mutation G1849T (V617F) with an allele-specific, quantitative, polymerase chain reaction (PCR) using an amplification refractory mutation system (ARMS). This is the first FDA-authorized test intended to help physicians in evaluating patients for suspected Polycythemia Vera (PV). However, the FDA specifically states that this test is not intended for a stand-alone diagnosis of an MPN, nor can it detect less common mutations for MPN such as an exon 12 mutation (FDA, 2017a).

A search for “MPL” and “CALR” on December 28, 2018 did not yield any results. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81175, 81176, 81219, 81270, 81402, 81403, 81450, 81455, 0017U, 0027U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

For Policy Titled: JAK2, CALR, MPL Mutation Analysis in Myeloproliferative Neoplasms
Mutation Analysis in Myeloproliferative Neoplasms AHS - M2101


FDA. (2017). Approved Drugs - Ipsogen JAK2 RGQ PCR Kit (WebContent). from Center for Drug EvaluationandResearch
https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm551474.htm

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm551474.htm


*For Policy Titled: Mutation Analysis in Myeloproliferative Neoplasms*
Mutation Analysis in Myeloproliferative Neoplasms AHS - M2101

Medical Director review 5/2019
Medical Director review 8/2019
Medical Director review 11/2019
Medical Director review 4/2020

Policy Implementation/Update Information

For Policy Titled: JAK2, CALR, MPL Mutation Analysis in Myeloproliferative Neoplasms

1/1/2019  New policy developed. BCBSNC will provide coverage for JAK2, CALR, MPL mutation analysis in myeloproliferative neoplasms when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

For Policy Titled: Mutation Analysis in Myeloproliferative Neoplasms

5/14/19   Reviewed by Avalon 1st Quarter 2019 CAB. Added related policies section. Under When Not Covered section B., removed statement: should first be tested for JAK2 mutations; if testing is negative, further testing to detect CALR and MPL mutation and for patient suspected to have ET.” Under When Not Covered section C, removed statement: should first be tested JAK2 mutations; if testing is negative further testing to detect CALR and MPL mutations, for patient suspected to have PMF.” Under When Not Covered section, added statement: “If testing five or more genes, refer to policy AHS-M2109 Molecular Panel Testing of Cancers to Identify Targeted Therapy.” Updated Policy Guidelines section. Added PLA codes 0017U and 0027U to Billing/Coding section. Title changed from “JAK2, CALR, MPL Mutation Analysis in Myeloproliferative Neoplasms” to “Mutation Analysis in Myeloproliferative Neoplasms.” Medical Director review 5/2019. (lpr)

10/1/19   Reviewed by Avalon 2nd Quarter 2019 CAB. Under “When Covered” section added: NOTE: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy. Deleted coding table from Billing/Coding section. Medical Director review 8/2019. (lpr)

12/31/19  Specialty Matched Consultant Advisory Panel review 11/20/2019. No change to policy statement. (lpr)

5/12/20   Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. Updated Description, Policy Guidelines, References. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.