Genetic Testing for FLT3 and NPM1 Mutations in Acute Myeloid Leukemia

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<tr>
<td>2.0 Medicine</td>
<td>January 1, 2015</td>
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<td>2.04 Pathology/Laboratory</td>
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**Description**

Treatment of acute myeloid leukemia (AML) is based on risk stratification, mainly patient age and tumor cytogenetics. The identification of mutations in several genes, including FLT3 and NPM1, have been proposed to allow for further segregation in the management of this heterogeneous disease.

**Related Policies**

- N/A

**Policy**

Genetic testing for FLT3 internal tandem duplication (FLT3/ITD) and NPM1 mutations may be considered medically necessary in cytogenetically normal AML (see Policy Guidelines section).

Genetic testing for FLT3 internal tandem duplication (FLT3/ITD) and NPM1 mutations is considered investigational in all other situations.

Genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) mutations is considered investigational.

Genetic testing for FLT3 or NPM1 mutations to detect minimal residual disease is considered investigational.

**Policy Guidelines**

This testing is intended to guide management decisions in patients who would receive treatment other than low-dose chemotherapy or best supportive care.

There are specific CPT codes for the following testing:

- **81245**: FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (i.e., exons 14, 15)

- **81310**: NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants

The following CPT code is specific to FLT3 tyrosine kinase domain (TKD) variants:

- **81246**: FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)
**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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

**Rationale**

**Background**

**Acute Myeloid Leukemia**

AML is a group of diverse hematologic malignancies characterized by the clonal expansion of myeloid blasts in the bone marrow, blood and/or other tissues. It is the most common type of leukemia in adults, and is generally associated with a poor prognosis. It is estimated that, in 2014, 18,860 people will be diagnosed with AML and 10,460 will die of the disease. The median age at diagnosis is 66 years, with approximately 1 in 3 of patients diagnosed at 75 years of age or older. (1)

**Diagnosis and Prognosis of AML**

The most recent World Health Organization (WHO) classification (2008) reflects the increasing number of acute leukemias that can be categorized based on underlying cytogenetic abnormalities (i.e., at the level of the chromosome including chromosomal translocations or deletions) or molecular genetic abnormalities (i.e., at the level of the function of individual genes, including gene mutations). These cytogenetic and molecular changes form distinct clinical-pathologic-genetic entities with diagnostic, prognostic, and therapeutic implications. (2) Conventional cytogenetic analysis (karyotyping) is considered to be a mandatory component in the diagnostic evaluation of a patient with suspected acute leukemia, as the cytogenetic profile of the tumor is considered to be the most powerful predictor of prognosis in AML and is used to guide the current risk-adapted treatment strategies. Younger adult patients are usually categorized into 3 different risk groups based on cytogenetics (good, intermediate, poor risk).

Molecular mutations have been analyzed to subdivide AML with normal cytogenetics into prognostic subsets. In AML, 2 of the most frequent molecular changes with prognostic impact are mutations of the FLT3 gene, encoding a receptor of tyrosine kinase involved in hematopoiesis and mutation of the NPM1 gene, encoding a shuttle protein within the nucleolus.

“AML with mutated NPM1” was included as a provisional entity in the 2008 WHO classification of acute leukemias. AML with FLT3 mutations is not considered a distinct entity in the 2008 classification, although the WHO recommends determining the presence of FLT3 mutations because of the prognostic significance. (2)
Recent reviews highlight the evolving classification of AML into distinct molecular subtypes. (1,3-5)

**Treatment**

AML has a highly heterogeneous clinical course, and treatment generally depends on the different risk-stratification categories. (1) Depending on the risk-stratification category, treatment modalities may include intensive remission induction chemotherapy, hypomethylating agents, clinical trials with innovative compounds, palliative cytotoxic treatment or supportive care only. For patients who achieve a complete remission (CR) after induction treatment, possible postremission treatment options include intensive consolidation therapy, maintenance therapy or autologous or allogeneic hematopoietic stem-cell transplantation (HSCT). (1)

**FLT3 Mutations**

FMS-like tyrosine kinase (FLT3) plays a critical role in normal hematopoiesis and cellular growth in hematopoietic stem and progenitor cells. Mutations in FLT3 are one of the most frequently encountered mutations in AML, and approximately 30% of AML patients harbor some form of FLT3 mutation. (6) FLT3 mutations are divided into 2 categories: (1) internal tandem duplications (FLT3/ITD) mutations, which occur in or near the juxtamembrane domain of the receptor, and (2) point mutations resulting in single amino acid substitutions within the activation loop of the tyrosine kinase domain (FLT3/TKD).

FLT3/ITD mutations are much more common than FLT3/TKD mutations, occurring in 25% of newly diagnosed adult cases of AML, versus FLT3/TKD mutations, occurring in about 7% of patients. FLT3/ITD are a well-documented adverse prognostic marker, particularly in patients younger than 60 years of age and with normal or intermediate risk cytogenetics, and is associated with an increased risk of relapse and inferior overall survival (OS). (6-8). Patients with FLT3/ITD mutations have a worse prognosis when treated with conventional chemotherapy, compared with patients with wild type (i.e., nonmutated) FLT3. Although remission can be achieved in patients with FLT3/ITD mutations using conventional induction chemotherapy at a frequency similar to other AML patients, the remission durations are shorter and relapse rates are higher. The median time to relapse in patients with a FLT3/ITD mutation is 6 to 7 months compared with 9 to 11 months in patients with other AML subtypes. (6) Once FLT3/ITD AML relapses, the disease is rapidly fatal.

Because of the high risk of relapse, hematopoietic stem-cell transplantation (HSCT) as consolidation of a first remission for a FLT3/ITD AML patient is often a consideration. However, this must be weighed against the treatment-related mortality associated with a transplant. (6)

FLT3 tyrosine kinase inhibitors (TKIs) are under active clinical investigation.

The prognostic impact of FLT3/TKD mutations is less certain, and has only been studied in small numbers of patients. (6, 9)

The clinical significance of an FLT3 mutation varies according to the nature of the mutation and the context in which it occurs. Longer FLT3/ITD mutations have been associated with reduced remission rates and/or worse survival in some studies. (6)

For FLT3/ITD mutations, allelic ratio refers to the number of ITD-mutated alleles compared with the number of WT (nonmutated) alleles. This ratio is influenced by the number of malignant versus benign cells in the sample tested and by the percentage of cells with 0, 1 or 2 mutated alleles. In most cases, the mutation detected at diagnosis is also present at relapse. However, in some cases, as FLT3/ITD-positive AML evolves from diagnosis to relapse, the mutation present at diagnosis may be absent (or undetectable) at relapse.
This is most commonly seen in cases in which the mutant allele burden is low (5%-15%) at diagnosis. (6) For this reason, and the overall lack of sensitivity of the assay (see Clinical Validity), the assay is considered to be unsuitable for use as a marker of minimal residual disease. (6) Higher mutant to WT allelic ratios have been associated with worse outcomes. (6)

**NPM1**

The most common molecular aberration in AML is a mutation of NPM1, which is found in 46% to 64% of cytogenetically normal AML (CN-AML) and 9% to 18% of cytogenetically abnormal AML. (1) Up to 50% of AML with mutated NPM1 also carry a FLT3/ITD. Mutated NPM1 confers an independent favorable prognosis for patients with CN-AML and either the presence or absence of a FLT3/ITD. Retrospective studies of banked clinical samples suggest that a NPM1 mutation may mitigate the negative prognostic effect of an FLT3/ITD, but possibly only if the FLT3/ITD to WT allelic ratio is low. (6) The prognostic impact in patients with an abnormal karyotype is unclear. (1)

**Regulatory Status**

No U.S. Food and Drug Administration (FDA) cleared genetic tests for FLT3 or NMP were found. Thus, these genetic tests are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

Clinically validated FLT3 mutation testing is performed with a polymerase chain reaction-based assay of genomic DNA isolated from the leukemic cells, either from the blood or bone marrow. Testing for FLT3 may involve a duplex assay which tests for both types of FLT3 mutations (ITD and TKD); however, some laboratories only test for ITD mutations, as the prognostic effect of TKD mutations is uncertain. (6)

Several laboratories offer these tests including Quest Diagnostics, Medical Genetic Laboratories of Baylor College, Geneva Labs of Wisconsin, LabPMM and ARUP Laboratories.

**Literature Review**

This policy was created in July 2014 and is based on a search of the MEDLINE database through June 11, 2014. Literature that describes the analytic validity, clinical validity, and clinical utility of genetic testing for FLT3 and NPM1 mutations was sought.

**Analytic validity** (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

No published data on the analytic validity of FLT3 or NPM1 mutation testing is identified.

**Clinical validity** (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

Published data on the clinical validity of FLT3 testing is lacking, however, a review article highlights that a major limitation of most polymerase chain reaction (PCR) assays for FLT3/ITD mutations is lack of sensitivity, compared with PCR assays for other acute myeloid leukemia (AML)–associated genetic alterations. (6) The sensitivity of the PCR assays is a function of the amount of sample DNA and the number of PCR cycles. However, for the FLT3/ITD assay, increasing the number of cycles does not increase the sensitivity because the PCR primers used to amplify the mutant allele also amplify the wild-type (WT) allele, and the shorter WT allele has a competitive advantage over the
mutant allele, because it takes more time to complete a PCR cycle for the longer-length mutant allele. The longer the mutation (insertion), the greater the PCR bias. (6)

This bias can be minimized using fewer PCR cycles, but this could affect the sensitivity if there is a low burden of leukemia cells in the sample. (6)

Published data on the clinical validity of testing for NPM1 mutations is not identified.

Clinical utility (how the results of the 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)

The clinical utility of molecular testing for FLT3 and NPM1 mutations is in whether such testing will change patient management and if this change in management will lead to improved patient outcomes.

The literature on the use of these markers consists of retrospective analyses, and no prospective studies have been published to date.

Most of the literature consists of analyses of FLT3/ITD mutations and survival outcomes with the use of allogeneic hematopoietic stem-cell transplantations (H SCT) in patients depending on the presence of this type of mutation. In general, the data support the use of H SCT in patients with FLT3/ITD mutations; however, not all studies have shown consistent results. (6)

Gale et al first reported the results of a retrospective analysis of FLT3 status in patients enrolled in 2 trials in the United Kingdom.(10) The trials included 1135 adult patients with AML, of whom 141 received autologous H SCT and 170 an allogeneic H SCT in first complete remission (CR), based on donor availability. An FLT3/ITD was detected in 283 of the total study population of 1135. Of the patients who underwent autologous H SCT (n=141), 37 (26%) were FLT3/ITD-positive and among those who received an allogeneic H SCT (n=170), 35 (21%) were FLT3/ITD-positive. The clinical investigators were not aware of FLT3/ITD status and did not direct treatment based on FLT3 mutation status. There was no difference in effect on relapse rate with the use of autologous versus allogeneic H SCT (odds ratio [OR], 2.39; confidence interval [CI], 1.24 to 4.62 for autologous; OR=1.31; CI, 0.56 to 3.06 for allogeneic; p=0.3), nor between patients who did or did not receive a transplant (p=0.4).

They performed an additional analysis of the effect of allogeneic H SCT in FLT3/ITD-positive patients, by performing a donor versus no donor analysis of 683 patients in whom FLT3/ITD status was available. No difference in relapse rate was noted in FLT3/ITD-positive versus negative patients (OR=0.70; CI, 0.53 to 0.92 vs OR=0.59; CI, 0.40 to 0.87; respectively; p=5). The authors concluded that their results suggest that there is no strong evidence that FLT3 status should influence the decision whether to proceed to transplant.

In 2012, Brunet et al retrospectively compared outcomes for FLT3/ITD AML patients registered in the European Group for Blood and Marrow Transplantation (EBMT) who underwent a myeloablative allogeneic H SCT in first remission, compared with patients without the mutation. (11) Of 1467 patients who met inclusion criteria (age 18 years or older, de novo AML, normal cytogenetics at diagnosis, myeloablative allogeneic H SCT performed between 2000 and 2008), 206 (14%) had FLT/ITD data. FLT/ITD was present in 120 patients, absent in 86. At 2 years, the relapse incidence was 30%±5% versus 16%±5% (p=0.006) in FLT3/ITD-positive versus FLT3/ITD-negative patients, and leukemia-free survival (LFS) 58%±5% versus 71%±6% (p=0.04), in FLT3-positive patients versus negative, respectively. Although the presence of FLT3/ITD led to a higher relapse risk and inferior LFS in this study when compared with the FLT3-negative patients, the observed 2-year LFS of
58% and the relapse risk of 30% in the patients with the FLT3/ITD mutation compares favorably with outcomes that have been reported in patients with FLT3/ITD mutations after postremission chemotherapy (i.e., that did not undergo transplant), which has been reported to have a median survival of 2.5 months.

Bomhauer et al reported the results of the AML 96 study of the DSIL (German study initiative leukemia) in which 999 patients 60 years of age or younger were prospectively included between 1996 and 2003 and stratified according to cytogenetic risk category. (12) Of patients with intermediate-risk cytogenetics, 555 were available for evaluation of FLT3 mutation status; 175 (31.5%) were FLT3/ITD positive. The rate of remission after 2 cycles of induction chemotherapy including high-dose Ara-C was not different in patients with and without FLT3/ITD (68% vs 63%). The investigators decided to determine the impact of different consolidation therapies on overall survival (OS) and the probability of relapse with respect to FLT3/ITD mutation status. Patients underwent allogeneic H SCT (n=103), autologous H SCT (n=141) if no donor was available, or conventional consolidation chemotherapy consisting of high-dose Ara-C (n=132) if the patient could not mobilize autologous cells. After a median follow-up of 53 months, OS was not significantly different between FLT3/ITD positive and negative patients having undergone autologous or allogeneic H SCT. In the group that received conventional consolidation chemotherapy, FLT3/ITD-positive patients had an inferior probability of survival (21% vs 46%; hazard ratio [HR], 2.2; 95% CI, 1.4 to 3.5; p=0.001), and the relapse probability was significantly higher in FLT3/ITD-positive versus negative patients (94% vs 59%; HR=4.0; 95% CI, 2.5 to 6.6; p<0.001).

Dezem et al reviewed the clinical data from November 2004 to October 2008 of 133 consecutive patients with previously untreated AML. (13) Patients were between the ages of 20 and 59 and received induction and consolidation therapy at Johns Hopkins, and were followed through August 2010. Thirty-one patients (23%) harbored an FLT3/ITD mutation. Induction success was similar between the 2 groups with 20 of 31 (65%) of FLT3/ITD mutation patients and 52/85 (61%) of WT patients. Of the 20 FLT3/ITD patients in complete remission (CR1), 11 (55%) underwent allogeneic H SCT, 9 myeloablative and 2 nonmyeloablative. The FLT3/ITD patients who did not undergo HSCT either did not have a suitable donor or had precluding comorbidities. Seventeen (33%) of the WT patients underwent H SCT in CR1; 14 myeloablative, 1 syngeneic, 1 autologous and 1 nonmyeloablative allogeneic. In the FLT3/ITD nontransplant group, median relapse-free survival was 8.6 months (range, 5.3-43.3 months) versus 54.1 months (range, 6.4-69.9 months) in the FLT3/ITD transplant group (p=0.03). Median OS in the WT, nontransplant group versus the WT, transplant group was 57.3 months (range, 3.9-64.4) versus 60 months, respectively (p=0.02). The authors conclude that their study suggests an advantage of H SCT in patients with FLT3/ITD in early CR1. However, the number of patients transplanted was small.

Willemze et al conducted a randomized trial in 1942 newly diagnosed patients with AML, age 15 to 60 years to compare remission induction treatment containing either standard or high-dose cytarabine. (14) In both arms, patients who achieved CR received consolidation therapy with either an autologous or allogeneic H SCT. Patients were subclassified as good risk, intermediate risk, bad risk, very bad risk or unknown risk, according to cytogenetics and FLT3/ITD mutation. Testing for FLT3/ITD mutation showed that in the standard dose cytarabine group, 50% were negative, 13% were positive, and 37% were unknown. In the high-dose cytarabine group, 48% were negative, 14% were positive, and 38% were unknown. All patients with a FLT3/ITD mutation were categorized as very bad risk. OS at 6 years in the patients categorized as very bad risk was 20% in the standard cytarabine group and 31% in the high-dose group (HR=0.70; 95% CI, 0.47 to
The authors concluded that patients with very bad risk cytogenetics and/or FLT3/ITD mutation benefitted from high-dose cytarabine induction treatment.

Pratcorona et al reported on the outcomes of 303 patients with intermediate-risk cytogenetics AML who were treated with intensive chemotherapy. They analyzed the effect of the ratio of FLT3/ITD to FLT3 WT, depending on the presence of an NPM1 mutation. FLT3/ITD mutations were identified in 94 (31%) of patients and NPM1 mutations in 161 (53%) of patients (65 patients harbored both mutations). To further confirm the prognostic value of the FLT3/ITD mutations to WT ratio, the patients were also subdivided into FLT3wt, FLT3-ITD/wt, ratio <0.5 (low ratio) and FLT3-ITD/wt ratio ≥0.5 (high ratio). The 0.5 cutoff value was chosen based on maximum clinical prognostic impact derived at that threshold as, in this series, this cutoff showed the greatest difference in relapse rate in patients with FLT3/ITD. Among the patients with NPM1 mutations, FLTwt and low ratio groups showed similar OS, relapse risk, and LFS. High ratio patients had a worse outcome. In patients without NPM1 mutations, FLT3/ITD subgroups showed comparable outcomes, with a higher risk of relapse and shortened OS than WT FLT3 patients.

**Clinical Trials**

No ongoing phase 3 trials comparing the outcomes of allogeneic or autologous HSCT depending on FLT3 or NPM1 mutation status are identified.

**Summary**

Acute myeloid leukemia (AML) is a heterogeneous disease and treatment is based on risk stratification, mainly by patient age and tumor cytogenetics (karyotyping), which allow for patients to be divided into good, intermediate, and poor risk categories. The identification of mutations in several genes, including FLT3 and NPM1, has been proposed to allow for further segregation of prognostic categories in the cytogenetically normal group.

FLT3/ITD mutations are known to confer a very poor prognosis, whereas NPM1 mutations have been shown to confer an independently favorable prognosis, and limited data suggest that a coexistent NPM1 mutation may mitigate the negative prognostic effect of an FLT3/ITD mutation, if both mutations are present. The prognostic effect of FLT3/TKD mutations is uncertain.

Data on the analytic and clinical validity of FLT3 and NPM1 mutation testing are lacking. Data on the clinical utility of testing for these mutations is limited to retrospective analyses, and consist predominantly of studies of the effect of the presence of a FLT3/ITD mutation in patients who underwent hematopoietic stem-cell transplant versus those who did not. Although some controversy exists as to the survival benefit in transplanting a patient with an FLT3/ITD mutation, retrospective studies, in general, have suggested a survival benefit in transplanting these poor risk patients, and major professional societies and guidelines recommend testing for these mutations for risk stratification and treatment management decisions, including possible hematopoietic stem-cell transplantation.

Therefore, genetic testing for FLT3 internal tandem duplication (FLT3/ITD) and NPM1 mutations may be considered medically necessary in cytogenetically normal AML, whereas genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) mutations is considered investigational.

**Practice Guidelines**

The 2014 National Comprehensive Cancer Network guidelines for Acute Myeloid Leukemia (16) (v 2.2014) provide the following recommendations:
For the evaluation and initial workup for suspected acute leukemias, bone marrow analysis with cytogenetics (karyotype) with or without fluorescence in situ hybridization (FISH) is necessary to establish the diagnosis of AML; cryopreservation of samples for evaluation of other markers, including FLT3-ITD and NPM1 mutations.

Evaluation of several molecular markers (e.g., FLT3, NPM1, CEBPA, and C-KIT) may be important for risk assessment and prognostication, and may also guide treatment decisions.

The American Society of Clinical Oncology states that classification of AML increasingly relies on genetic analysis and that broad-based mutation profiling of AML will be helpful in defining important prognostic subgroups and may contribute to the selection of patients for enrollment into trials with novel inhibitors.

The Alberta Provincial Hematology Tumour Team issued a 2009 guideline on acute myeloid leukemia that includes the recommendation for molecular analysis in cases with normal karyotypes, including FMS-like tyrosine kinase 3 (FLT3).

**U.S. Preventative Services Taskforce**

Genetic testing for FLT3 and NPM is not a preventive service.

**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**

10. Gale RE, Hills R, Kottaridis PD et al. No evidence that FLT3 status should be considered as an indicator for transplantation in acute myeloid leukemia (AML):


**Documentation Required for Clinical Review**

- History and physical, including:
  - Reason for testing
  - Lab reports, demonstrating determined:
    - Cytogenetic analysis
    - NMP mutation
    - Determined FLT3/ITD mutations

**Coding**

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

**MN/IE**

The following service/procedure may be considered medically necessary in certain instances and investigational in others. Services may be medically necessary when...
policy criteria are met. Services are considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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**Policy History**

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

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<td>Medical Policy Committee</td>
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<tr>
<td>1/1/2015</td>
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<td>Administrative Review</td>
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**Definitions of Decision Determinations**

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

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

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

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

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

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

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

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

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