Chimeric Antigen Receptor T cell Therapy (CAR-T)

Policy # 00605
Original Effective Date: 02/21/2018
Current Effective Date: 09/19/2018

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: Other forms of adoptive immunotherapy such as using adoptive cellular therapy for the administration of cytotoxic T lymphocytes, cytokine-induced killer cells, tumor-infiltrating lymphocytes, or antigen-loaded autologous dendritic cells are addressed separately in medical policy 00248.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Acute Lymphoblastic Leukemia

Based on review of available data, the Company may consider the use of tisagenlecleucel (Kymriah™)‡ for the treatment of relapsed or refractory B cell acute lymphoblastic leukemia (ALL) to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility for the use of tisagenlecleucel (Kymriah) will be considered when all of the following criteria are met:

- Patient has a confirmed diagnosis of CD19-positive B-cell ALL with morphologic bone marrow tumor involvement (≥5% lymphoblasts); AND
- Patient is 25 years old or younger at time of infusion; AND
- Disease is refractory to initial therapy or in second or later relapse
    - Refractory is defined as failure to obtain complete response with induction therapy, i.e., failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts);
    - Relapsed is defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission (CR) with chemotherapy and/or allogeneic stem cell transplant; AND
- Patient has NOT received prior treatment with Kymriah or any other cellular immunotherapy and is not being considered for treatment with any other cellular immunotherapy; AND
  *(Note: This specific criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This specific criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

- Patient does NOT have any of the following:
  - Burkitt lymphoma; OR
  - Active hepatitis B virus, hepatitis C virus, or other uncontrolled fungal, bacterial, or viral infection requiring intravenous antimicrobials; OR
  - Grade 2-4 graft-vs-host disease; OR
  - Concomitant genetic syndrome with the exception of Down syndrome; OR
  - Received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion; OR
  - Active central nervous system (CNS) disease defined by the National Comprehensive Cancer Network (NCCN) guidelines to be a presence of ≥ 5 white blood cells (WBC) per microliter (µL) in the cerebrospinal fluid (CSF) in addition to the presence of lymphoblasts.
    *(Note: These criteria are additional company requirements for coverage eligibility and will be denied as not medically necessary** if not met)*

B-cell Lymphoma

Based on review of available data, the Company may consider the use of axicabtagene ciloleucel (Yescarta™)‡ or tisagenlecleucel (Kymriah) for the treatment of relapsed or refractory B-cell lymphoma to be **eligible for coverage.**

Patient Selection Criteria

Coverage eligibility for the use of axicabtagene ciloleucel (Yescarta) or tisagenlecleucel (Kymriah) will be considered when all of the following criteria are met:

- Patient has a documented diagnosis of one of the following:
  - Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; OR
  - Primary mediastinal large B-cell lymphoma (Yescarta only); OR
    (Note: Kymriah is considered investigational for the treatment of primary mediastinal large B-cell lymphoma)*
  - High grade B-cell lymphoma; OR
  - DLBCL arising from follicular lymphoma; AND
- Patient is ≥ 18 years old at the time of infusion; AND
- Disease is relapsed or refractory, defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant); AND
- Patient has failed two or more lines of systemic therapy including:
  - Anti-CD20 monoclonal antibody (such as rituximab) unless tumor is CD20-negative; AND
  - An anthracycline containing chemotherapy regimen; AND

  *(Note: The criteria requiring specific systemic agents are additional company requirements for coverage eligibility and will be denied as not medically necessary** if not met. If patient has not failed two or more lines of any systemic therapy, request will be denied as investigational*)*

- Patient has NOT received prior CD19-directed chimeric antigen receptor T cell therapy (CAR-T) treatment or any other genetically modified T cell therapy and is not being considered for treatment with any other cellular immunotherapy; AND
  *(Note: This criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  *(Note: This criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient does NOT have ANY of the following:
  - Primary CNS lymphoma; OR
  - Active CNS disease (e.g. seizure disorder, cardiovascular [CV] ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement); OR
    *(Note: This criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
  - Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or other uncontrolled fungal, bacterial, or other viral infection requiring intravenous antimicrobials

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of tisagenlecleucel (Kymriah) or axicabtagene ciloleucel (Yescarta) when the patient has received prior treatment with CAR-T or other cellular immunotherapy, when the patient does not have adequate organ function, or has active CNS disease to be **not medically necessary.****

Based on review of available data, the Company considers the use of tisagenlecleucel (Kymriah) for the treatment of ALL when the patient has Burkitt lymphoma, has a concomitant genetic syndrome (other than Down syndrome), has grade 2-4 graft-vs-host disease, or has received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion to be **not medically necessary.****

Based on review of available data, the Company considers the use of axicabtagene ciloleucel (Yescarta) or tisagenlecleucel (Kymriah) when the patient has not failed at least one anti-CD20 monoclonal antibody (unless tumor is CD20 negative), has not failed an anthracycline containing chemotherapy regimen, to be **not medically necessary.****

Chimeric Antigen Receptor T cell Therapy (CAR-T)

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When 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 the use of tisagenlecleucel (Kymriah) or axicabtagene ciloleucel (Yescarta) when patient selection criteria are not met (except those listed as not medically necessary**) to be **investigational.***

Background/Overview

CAR-T is a form of cellular immunotherapy in which a patient's own T cells are removed and programmed to destroy cells marked with a certain protein. In the case of Kymriah and Yescarta, that protein is CD-19 which is expressed on most B cells. These drugs are therefore indicated for certain cancers involving proliferation of B cells.

Kymriah is a CAR-T therapy approved for the treatment of relapsed or refractory ALL in patients younger than 25 years of age and for the treatment of adults with relapsed or refractory large B-cell lymphoma. Treatment involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing cells. The patient's T cells are removed and reprogrammed *in vitro* then re-infused at a rate of 10-20 mL/min. The recommended dosage of Kymriah for patients with B-cell ALL who are 50 kg or less is 0.2 to 5.0×10^6 CAR- positive viable T cells per kilogram of body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5×10^8 total CAR-positive viable T cells (non-weight-based) intravenously. The recommended dose of Kymriah for patients with large B-cell lymphoma is 0.6 to 6.0 $x10^8$ CAR-positive viable T cells intravenously. Prior to infusion, the patient must be pre-treated with fludarabine and cyclophosphamide to deplete the patient's lymphocytes and reduce the risk of severe cytokine release syndrome (CRS). CRS is one of the most common adverse effects occurring in 79% of patients in the ALL pivotal trial. Severe CRS may be life-threatening and should be treated with tocilizumab. Due to the potential for severe CRS, the drug is only available through a Risk Evaluation and Mitigation Strategy (REMS) program to ensure that providers are aware of the signs of CRS and able to appropriately treat severe CRS.

Yescarta is a CAR-T therapy currently approved for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy. Similar to Kymriah, Yescarta is a cellular immunotherapy in which the T cells of a patient are modified genetically to selectively target and bind to CD19 antigen expressed on the surface of normal and malignant B cells. Prior to infusion of Yescarta, the patient must be pre-treated with a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine. The recommended dosage of Yescarta is 2×10^6 CAR-positive viable T cells per kilogram body weight with a maximum of 2×10^8 CAR-positive viable T cells. After infusion of Yescarta, patients must be monitored at least daily for 7 days at a certified healthcare facility for signs and symptoms of CRS and neurologic toxicities and then remain within proximity of the certified healthcare facility for at least 4 weeks following infusion. As with Kymriah, CRS occurs frequently in Yescarta-treated patients resulting in the drug being restricted through a REMS program. Both the Kymriah and the Yescarta REMS programs require health care facilities that dispense and administer the drugs to comply with the following requirements:

- Certified facilities must have onsite, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for administration within 2 hours after Kymriah or Yescarta infusion, if needed for treatment of CRS.
- Certified facilities must ensure that health care providers who prescribe, dispense, or administer Kymriah or Yescarta are trained to manage CRS and neurologic toxicities.

Acute lymphoblastic leukemia (ALL)
ALL is one of the most common childhood malignancies. Despite having a relatively high 5 year overall survival rate of 85%, prognosis is poor for those who do not respond to initial treatment. Relapse following ALL treatment is the second most common cause of cancer-related death in children. Initial treatment is approached in three stages: induction, consolidation, and maintenance. The goal of induction therapy, which usually lasts 3-4 weeks, is to achieve an initial CR. If CR is not reached during this stage, the disease is considered refractory. Consolidation treatment is designed to prevent leukemic regrowth, reduce residual tumor burden, and prevent emergence of drug resistance in the remaining leukemic cells. This phase typically lasts 4-8 months and includes drugs tailored to the patient based on risk of re-occurrence. The final phase of treatment, the maintenance phase, is a less intensive continuation regimen of daily therapy that is continued for a total treatment duration of 30-42 months. Re-occurrence after completion of the maintenance phase is considered relapse and requires aggressive reinduction therapy and intensification, which is often ineffective. Patients who achieve a second remission are candidates for allogeneic hematopoietic stem cell transplantation (HSCT). Relapse of ALL can occur in many extramedullary sites, but most often occurs in the bone marrow, CNS, or testicles. Bone marrow relapse is the most common site of relapse and usually presents with persistent peripheral blood cytopenias. When the relapse occurs in the CNS, the NCCN guidelines classify the disease into the following categories:

- CNS 1: No lymphoblasts in CSF regardless of the WBC count;
- CNS 2: WBC<5/µL in CSF with presence of lymphoblasts;
- CNS 3: WBC $\geq$5/µL in CSF with presence of lymphoblasts.

Current NCCN guidelines for ALL recommend (category 2A) Kymriah as a treatment option for:
- Philadelphia chromosome-positive patients 26 years or less in age with refractory disease or 2 or more relapses and failure of 2 tyrosine kinase inhibitors.
- Philadelphia chromosome-negative patients 26 years or less in age with refractory disease or 2 or more relapses.

Diffuse large B-cell lymphoma (DLBCL)
DLBCL is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases. DLBCL exhibits large heterogeneity in morphologic, genetic, and clinical aspects and multiple clinicopathologic entities are defined by the 2016 World Health Organization classification, which are sufficiently distinct to be considered separate diagnostic categories.

It has been estimated that 27,650 new cases of DLBCL were diagnosed in the United States in 2016. Treatment in the first-line setting (particularly rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) is associated with a 5-year survival rate ranging from 60-70%. However, based on a number of prognostic factors, 20-50% of DLBCL cases are refractory or relapse after first-line chemotherapy. The response to subsequent salvage chemotherapy and consolidation with autologous cell transplantation is suboptimal with one study finding only 7% of patients with refractory DLBCL achieving a complete response to the next line of therapy.

Current NCCN guidelines for B-cell lymphomas recommend (category 2A) Yescarta or Kymriah as a treatment option:

- For histological transformation to DLBCL after multiple lines of prior therapies which includes ≥2 chemo-immunotherapy regimens for indolent or transformed disease.
- For relapse or refractory disease DLBCL after multiple lines of prior therapies which includes ≥2 chemo-immunotherapy regimens for indolent or transformed disease.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

On August 30, 2017, Kymriah was approved by the FDA for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

On May 1, 2018, Kymriah was approved by the FDA for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCBL arising from follicular lymphoma.

On October 18, 2017, Yescarta was approved by the FDA for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Kymriah was approved for ALL based on an open-label, multicenter single-arm trial including 63 patients treated with lymphodepleting chemotherapy followed by a single dose of Kymriah. Efficacy endpoints included achievement of CR within 3 months after infusion, duration of CR, and proportion of patients with CR and minimal residual disease (MRD) <0.01% by flow cytometry. CR designation required remission status to be maintained for at least 28 days without clinical evidence of relapse. 83% of patients achieved a

CR or CR with incomplete blood count recovery (CRi), and all patients were negative for MRD. Median duration of remission was not reached at the time that the study data was submitted (median follow-up of 4.8 months from response).

Patients were only included in the study if they had adequate organ function defined based on measures of serum creatinine, alanine aminotransferase (ALT), bilirubin, pulse oxygenation, and left ventricular ejection fraction. In addition, Kymriah was not studied in patients with extra-medullary disease relapse, Burkitt lymphoma, or concomitant genetic syndromes that pre-dispose patients to leukemia, such as Fanconi anemia or Kostmann syndrome. Patients with Down syndrome were not excluded.

It is important to note that adequate organ function was defined as follows:

- Serum Creatinine within normal limits for patient age

Age (years)	Serum Creatinine (mg/dL)
1-<2	≤0.6
2 - <6	≤0.8
6-<10	≤1
10-<13	≤1.2
13-<16	≤1.5 (Male) ≤1.4 (Female)
≥16	≤1.7 (Male) ≤1.4 (Female)

- ALT <5 times the upper limit of normal (ULN) for age
- Bilirubin <2.0 mg/dL
- Minimum level of pulmonary reserve < Grade 1 dyspnea and pulse oxygenation >91% on room air
- Left Ventricular Shortening Fraction >28% confirmed by echocardiogram or Left Ventricular Ejection Fraction >45% confirmed by echocardiogram or Multiple Uptake Gated Acquisition

Kymriah was approved for the treatment of relapsed or refractory B-cell lymphoma based on the open-label, multicenter, single-arm, JULIET trial. Studied patients were ≥18 years of age with relapsed or refractory DLBCL, who received ≥2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous HSCT. The study excluded patients with active CNS malignancy, prior allogenic HSCT, an ECOG performance status ≥2, a creatinine clearance <60, ALT >5 times normal, cardiac ejection fraction <45%, or absolute lymphocyte concentration less than 300/µL. Following 2 to 11 days after completion of lymphodepleting chemotherapy, Kymriah was administered as a single intravenous infusion. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden. Lymphodepleting chemotherapy could be omitted if the white blood cell count was <1000 cells/µL. The major efficacy outcomes were objective response rate per Lugano criteria as assessed by an independent review committee and duration of response. Of the 160 patients enrolled, 106 patients received Kymriah, including 92 patients who received product manufactured in the U.S. and were followed for at least 3 months or discontinued earlier. Eleven out of the 160 patients enrolled did not receive the drug

due to manufacturing failure. 38 other patients did not receive Kymriah, primarily due to death (n=16), physician decision (n=16), and adverse events (n=3). A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Patients included in this sub-group had either had no bridging chemotherapy, or had imaging that showed measurable disease after completion of bridging chemotherapy prior to Kymriah infusion. Of the 24 patients not included, 8 had no evidence of disease at baseline prior to Kymriah infusion, 15 did not have baseline imaging following bridging chemotherapy, and 1 was excluded because of initial misclassification of a neuroendocrine tumor as DLBCL.

Among the efficacy evaluable population of 68 patients, the median time to first response was 0.9 months. The median duration of response was not reached. Response durations were longer in patients who achieved complete response, as compared to patients with a best response of partial response. Of the 22 patients who experienced a complete response, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after Kymriah infusion. The overall response rate which includes complete and partial responses was 50% with a complete response rate of 32% and partial response rate of 18%.

Yescarta was approved based on the results of an open-label, multicenter phase 1/2 study, which reported CR rates and duration of response demonstrated in the phase 2 portion of the study. Adults with aggressive B-cell non-Hodgkin lymphoma that was primary refractory, refractory to a second or greater line of therapy, or relapsed within 1 year after autologous hematopoietic cell transplantation were enrolled in the study. Patients with prior allogeneic hematopoietic cell transplantation, any history of CNS lymphoma, Eastern Cooperative Oncology Group Performance Status score of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the ULN, cardiac ejection fraction less than 50%, or active serious infection were excluded. Most patients (74%) had de novo DLBCL and 32% had double- or triple-hit lymphoma. The median age was 58, with 24% being aged 65 years or older; the median number of prior therapies was 3; 77% had refractory disease to a second or greater line of therapy; and 21% had relapsed within 1 year after autologous hematopoetic cell transplantation (HCT).

All patients received a lymphodepleting regimen consisting of cyclophosphamide and fludarabine prior to infusion of Yescarta. Of the 111 patients who underwent leukapheresis, 101 received the infusion (9 were not treated due to progressive disease or serious adverse reactions following leukapheresis and there was a manufacturing failure in 1 patient). Study protocol mandated hospitalization of patients for infusion and 7 days after infusion. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. The median time from leukapheresis to product delivery was 17 days. The primary end point was objective response rate based on a modified intention-to-treat population, which was defined as all patients treated with at least 1.0×10^6 CAR-T cells per kilogram. Objective response was seen in 72% of patients with 51% achieving a complete response and 21% achieving a partial response.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Adoptive Immunotherapy”, 8.01.01, July 2018.
2. Tisagenlecleucel (Kymriah) [Package Insert]. Novartis. East Hanover, New Jersey Updated Aug 30, 2017.
3. Axicabtagene ciloleucel (Yescarta) [Package Insert]. Kite Pharma Inc. Updated Oct 18, 2017.

4. Swerdlow SH, Camp E, Pileri SA, et al. The 2016 revision of the World health Organization classification of lymphoid neoplasms. *Blood*. May 19 2016;127(20):2375-2390.
5. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World health Organization subtypes. *CA Cancer J Clin.* Sep 12 2016;66(6):443-459.
6. International Non-hodgkin's Lymphoma Prognostic Factors P. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* Sep 30 1993;329(14):987-994.
7. Sehn Lh, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood.* Mar 01 2007;109(5):1857-1861.
8. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood.* Oct 19 2017;130(16):1800-1808.
9. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: acute lymphoblastic leukemia. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf
10. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: B-cell lymphomas. Version 4.2018. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

Policy History

Original Effective Date: 02/21/2018
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02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. New policy
04/01/2018	Coding update
05/22/2018	Coding update
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. Updated criteria for Kymriah to include coverage for new B-cell lymphoma indication. Updated background information and references to reflect the most current literature.

Next Scheduled Review Date: 09/2019

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 2017 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:

Code Type	Code
CPT	No codes
HCPCS	C9399, J3490, J3590, J9999, Q2040,S2107 Code added eff 4/1/18: Q2041
ICD-10 Diagnosis	C82.00- C82.49, C82.50- C82.59 , C82.60- C82.69, C82.80 -C82.89, C82.90- C82.99, C83.30-C83.37, C83.50 -C83.59, C85.20 -C85.29,C91.00-C91.02

*****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.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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