

MEDICAL POLICY – 8.01.01

Adoptive Immunotherapy

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RELATED MEDICAL POLICIES:

8.01.53 Cellular Immunotherapy for Prostate Cancer

8.01.520 Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Select a hyperlink below to be directed to that section.

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Introduction

The immune system is made up of several different disease-fighting cells. In cancer, however, the immune system sometimes either doesn't work as it should or the cancer cells are able to hide from the immune system. One therapy that draws on the immune system's natural fighting ability is called adoptive immunotherapy. In this technique, certain types of immune system cells are withdrawn from the person to be treated. They're re-engineered in a lab and given back to the patient in the hope that they will be better able to attack and defeat cancer cells. This is an active area of study. The U.S. Food and Drug Administration has approved two adoptive immunotherapy treatments, Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel). The FDA has approved them for people of certain ages who have specific types of cancer. This policy describes when these treatments may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Treatment	Medical Necessity
<p>Kymriah™ (tisagenlecleucel)</p>	<p>Kymriah™ (tisagenlecleucel) intravenous infusion is considered medically necessary for relapsed^a or refractory^b patients if they meet all of the following criteria:</p> <ul style="list-style-type: none"> • Confirmed diagnosis of CD19-positive B-cell acute lymphoblastic leukemia with morphologic bone marrow tumor involvement (≥5% lymphoblasts) • Are up to 25 years old at the time of infusion • Have not received prior treatment with tisagenlecleucel or any other gene therapy or are being considered for treatment with any other gene therapy • Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis • Do not have any of the following: <ul style="list-style-type: none"> ○ Burkitt lymphoma ○ Active hepatitis B, C, or any uncontrolled infection ○ Grade 2 to 4 graft-versus-host disease ○ Concomitant genetic syndrome with the exception of Down syndrome ○ Received allogeneic cellular therapy, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion ○ Patient has active central nervous system 3 (see Related Information) acute lymphoblastic leukemia (ie, white blood cell count ≥5 cells/μL in cerebrospinal fluid with presence of lymphoblasts). <p>Note: ^a Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission with chemotherapy and/or allogeneic cell transplant.</p> <p>^b Refractory (resistant) disease is defined as those patients who fail to obtain complete response with induction therapy, ie, 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).</p>



Treatment	Medical Necessity
<p>Yescarta™ (axicabtagene ciloleucel)</p> <p>Kymriah™ (tisagenlecleucel)</p>	<p>Yescarta™ (axicabtagene ciloleucel) or Kymriah™ (tisagenlecleucel) intravenous infusion (except as indicated^c) is considered medically necessary for relapsed or refractory^d patients if they meet all of the following criteria:</p> <ul style="list-style-type: none"> • Are adults (age ≥18) at the time of infusion • Histologically confirmed diagnosis of diffuse large B-cell lymphoma, not otherwise specified; or primary mediastinal large B-cell lymphoma^c or high-grade B-cell lymphoma or diffuse large B-cell lymphoma arising from follicular lymphoma • Received adequate prior therapy including all of the following: <ul style="list-style-type: none"> ○ Anti-CD20 monoclonal antibody for CD20-positive tumor ○ Anthracycline-containing chemotherapy regimen ○ For subjects with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma • Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist • Have not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy or are being considered for treatment with any other gene therapy. <p>AND</p> <ul style="list-style-type: none"> • Do not have primary central nervous system lymphoma <p>Note: ^c Tisagenlecleucel intravenous infusion is considered investigational for the treatment of relapsed or refractory primary mediastinal large B-cell lymphoma.</p> <p>^d Relapsed or refractory disease is defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant).</p>

Treatment	Investigational
<p>Other applications</p>	<p>Other applications of adoptive immunotherapy are considered investigational.</p>



Documentation Requirements

The patient's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

For Kymriah™ (tisagenlecleucel) for relapsed or refractory patients and ALL of the following:

- Confirmed diagnosis of B-cell acute lymphoblastic leukemia with CD19 tumor expression
- 25 years of age or younger at the time of infusion
- Have not received prior treatment with tisagenlecleucel or any other gene therapy, nor is being considered for treatment with any other gene therapy
- Have adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis (collection of blood)
- Do not have any of the following:
 - Burkitt lymphoma
 - Active hepatitis B, C, or any uncontrolled infection
 - Grade 2 to 4 graft-versus-host disease
 - The presence of a genetic syndrome, with the exception of Down syndrome
 - Received cellular therapy from a donor, such as donor lymphocyte infusion, within 6 weeks prior to tisagenlecleucel infusion
 - Patient has active central nervous system 3 acute lymphoblastic leukemia (ie, white blood cell count 5 or greater cells/ μ L in cerebrospinal fluid with presence of lymphoblasts)

For Yescarta™ (axicabtagene ciloleucel) and Kymriah™ (tisagenlecleucel) necessary for relapsed or refractory patients and ALL of the following:

- Adults (age 18 or older) at the time of infusion
- Tissue tests confirm the diagnosis of one of the following:
 - Diffuse large B-cell lymphoma, not otherwise specified, or
 - Primary mediastinal large B-cell lymphoma, or
 - High-grade B-cell lymphoma, or
 - Diffuse large B-cell lymphoma arising from follicular lymphoma
- Have received adequate prior therapy
- Have adequate organ and bone marrow function as determined by the treating oncologist/hematologist
- Have not received prior CD19-directed CAR T-cell therapy treatment or any other gene therapy, nor is being considered for treatment with any other gene therapy
- Do not have primary central nervous system lymphoma

Coding



Code	Description
CPT	
36511	Therapeutic apheresis; for white blood cells
HCPCS	
Q2040	Tisagenlecleucel (Kymriah™), up to 250 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per infusion (code terminated 1/1/19)
Q2041	Axicabtagene ciloleucel (Yescarta™), up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose (new code effective 4/1/18)
Q2042	Tisagenlecleucel (Kymriah™), up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose (new code effective 1/1/19)
S2107	Adoptive immunotherapy ie, development of specific antitumor reactivity (eg, tumor-infiltrating lymphocyte therapy) per course of treatment
Non-Covered	
These codes are not separately reimbursable	
0537T	Chimeric antigen receptor T-cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day (new code effective 1/1/19)
0538T	Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage) (new code effective 1/1/19)
0539T	Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration (new code effective 1/1/19)
0540T	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous (new code effective 1/1/19)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Autologous lymphocytes used as part of adoptive immunotherapy may be harvested in a pheresis procedure or may be isolated from resected tumor tissue.



The recommended dosage of tisagenlecleucel for patients with B-cell acute lymphoblastic leukemia who are 50 kg or less is 0.2 to 5.0×10^6 chimeric antigen receptor–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 chimeric antigen receptor–positive viable T cells (non-weight-based) intravenously.

The recommended target dose of tisagenlecleucel for patients with large B-cell lymphoma is 0.6 to 6.0×10^8 chimeric antigen receptor–positive viable T cells intravenously.

The recommended target dose of axicabtagene ciloleucel for patients with large B-cell lymphoma is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 chimeric antigen receptor–positive viable T cells intravenously.

Central nervous system (CNS) disease for B-cell acute lymphoblastic leukemia is defined by the following groups:

- CNS 1: Absence of blasts on cerebrospinal fluid cytopsin preparation, regardless of the white blood cell (WBC) count
- CNS 2: WBC count of less than 5/mL and blasts on cytopsin findings
- CNS 3: WBC count of 5/mL or more and blasts on cytopsin findings and/or clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome)

Tisagenlecleucel and axicabtagene ciloleucel have black box warnings because of the risks of cytokine release syndrome and neurologic toxicities that include fatal or life-threatening reactions. They should not be administered to patients with active infection or inflammatory disorders. It is recommended that severe or life-threatening cytokine release syndrome be treated with tocilizumab. Patients should be monitored for neurologic events after treatment.

Tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) are available only through a restricted program under a risk evaluation and mitigation strategy (REMS) called the Kymriah REMS and Yescarta REMS, respectively. The requirement for the REMS components are as follows:

- Health care facilities that dispense and administer tisagenlecleucel or axicabtagene ciloleucel must be enrolled and comply with the REMS requirements.
- Certified health care 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 tisagenlecleucel or axicabtagene ciloleucel infusion, if needed for treatment of cytokine release syndrome.



- Certified health care facilities must ensure that health care providers who prescribe, dispense, or administer tisagenlecleucel or axicabtagene ciloleucel are trained to manage cytokine release syndrome and neurologic toxicities.

Consideration of Age

The ages noted in the policy statements are based on the FDA labeling for these agents.

Evidence Review

Description

The spontaneous regression of certain cancers (eg, renal cell carcinoma, melanoma) supports the idea that a patient's immune system can delay tumor progression and, on rare occasions, can eliminate tumors altogether. These observations have led to research into various immunologic therapies designed to stimulate a patient's own immune system. Adoptive immunotherapy is a method of activating lymphocytes and/or other types of cells for the treatment of cancer and other diseases. Cells are removed from the patient, processed for some period of time, and then infused back into the patient.

Background

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a malignancy (clonal) of the bone marrow in which the early lymphoid precursors of the white blood cells (called lymphoblasts) proliferate and replace the normal hematopoietic cells of the marrow. This results in overcrowding of the bone marrow, as well as the peripheral organs (particularly the liver, spleen, and lymph nodes) by the lymphoblasts. As a consequence, the leukemic blasts displace the normal hematopoietic bone marrow and cause cytopenias in all three cell lineages (anemia, thrombocytopenia, granulocytopenia). Leukostasis affecting brain and lung may also occur. Death occurs commonly due to severe pancytopenia and resulting infections. Refractory (resistant) disease is defined as those patients who fail to obtain a complete response with induction therapy, ie, 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 disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission. Minimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. MRD positivity is defined as the presence of 0.01% or more ALL cells and has been shown to be a strongest prognostic factor to predict the risk of relapse and death when measured during and after induction therapy in both newly diagnosed and relapsed ALL. In a meta-analysis of 20 studies of 11,249 pediatric ALL, Berry et al (2017) reported a hazard ratio for event-free survival in MRD-negative patients compared with MRD-positive patients of 0.23 (95% confidence interval, 0.18 to 0.28).¹

Approximately 5000 cases of B-cell ALL are diagnosed every year in the United States,² and approximately 620 pediatric and young adult patients with B-cell ALL will relapse each year in the United States.³ B-cell ALL is largely a disease of the young, with approximately 60% of cases occurring in patients younger than 20 years old with a median age at diagnosis of 15 years.²

Treatment

While treatable in 85% cases, approximately 15% of children and young adults with ALL will relapse and 2% to 3% of ALL patients are primary refractory.⁴ Retreatment of refractory or relapsed ALL is generally unsuccessful and associated with a high mortality rate.⁵ The 2-year survival rate among patients with ALL who relapse after hematopoietic cell transplantation is 15%.⁶ The Food and Drug Administration (FDA) approved clofarabine (as a single agent or in combination) in 2004 and blinatumomab in 2014 for relapsed and refractory ALL. Reported median objective response rates in the pivotal trials of the 2 agents were 19.7% and 33%, the median durations of response were 2.5 months and 6 months, and median overall survival durations were 3 months and 7.5 months, respectively.^{7,8} Note that the percentages of patients treated with 3 or more prior treatments of clofarabine and blinatumomab trial were 62% and 7%, respectively. Nevertheless, treatment options for patients with relapsed or refractory ALL are limited, associated with poor outcomes and high toxicity and the disease remains incurable.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases.⁹ 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. Teras et al (2016) has estimated that 27,650 new cases of DLBCL were diagnosed in the United States in 2016.¹⁰

Treatment

Treatment in the first-line setting (particularly rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) is associated with a 5-year survival rate ranging from 60% to 70%.¹¹ However, based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy.^{12,13} The response to subsequent salvage chemotherapy and consolidation with autologous cell transplantation is suboptimal. A retrospective analysis of the SCHOLAR-1 study by Crump et al (2017), which pooled data from 2 phase-3 clinical trials and 2 observational cohorts, included 636 patients with refractory DLBCL.¹⁴ The objective response rate to the next line of therapy was 26%, with 7% achieving a complete response. Median overall survival was 6.3 months and 2-year survival 20%. Refractory DLBCL was defined as progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or as relapse 12 or fewer months after autologous cell transplantation.

Adoptive Immunotherapy

Adoptive immunotherapy uses “activated” lymphocytes as a treatment modality. Both nonspecific and specific lymphocyte activation are used therapeutically. The nonspecific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), also called autolympocyte therapy, increases the number of activated lymphocytes.

T Lymphocytes and Killer Cells

Initially, this treatment was performed by harvesting peripheral lymphokine-activated killer cells and activating them in vitro with the T-cell growth factor interleukin-2 (IL-2) and other cytokines. More recent techniques have yielded select populations of cytotoxic T lymphocytes with specific reactivity to tumor antigens. Peripheral lymphocytes are propagated in vitro with antigen-presenting dendritic cells (DC) that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with interleukin-2 and anti-CD3 antibody, a T-cell activator. Expansion of TIL for clinical use is labor



intensive and requires laboratory expertise. Only a few cancers are infiltrated by T cells in significant numbers; of these, TIL can be expanded in only approximately 50% of cases. These factors limit the widespread applicability of TIL treatment. Recently, cytokine-induced killer cells have been recognized as a new type of anti-tumor effector cells, which can proliferate rapidly in vitro, with stronger anti-tumor activity and a broader spectrum of targeted tumors than other reported anti-tumor effector cells.¹⁵

Cellular Therapy and Dendritic Cell Infusions

The major research challenge in adoptive immunotherapy is to develop immune cells with anti-tumor reactivity in quantities sufficient for transfer to tumor-bearing patients. In current trials, two methods are studied: adoptive cellular therapy and antigen-loaded dendritic cell infusions.

Adoptive cellular therapy is “the administration of a patient’s own (autologous) or donor (allogeneic) anti-tumor lymphocytes following a lymphodepleting preparative regimen.”¹⁶ Protocols vary, but include these common steps:

1. Lymphocyte harvesting (either from peripheral blood or from tumor biopsy)
2. Propagation of tumor-specific lymphocytes in vitro using various immune modulators
3. Selection of lymphocytes with reactivity to tumor antigens with enzyme-linked immunosorbent assay
4. Lymphodepletion of the host with immunosuppressive agents
5. Adoptive transfer (ie, transfusion) of lymphocytes back into the tumor-bearing host

DC-based immunotherapy uses autologous DC (ADC) to activate a lymphocyte-mediated cytotoxic response against specific antigens in vivo. ADCs harvested from the patient are either pulsed with antigen or transfected with a viral vector bearing a common cancer antigen. The activated ADCs are then retransfused back into the patient, where they present antigen to effector lymphocytes (CD4-positive T cells, CD8-positive T cells, and in some cases, B cells). This initiates a cytotoxic response against the antigen and against any cell expressing the antigen. In cancer immunotherapy, ADCs are pulsed with tumor antigens; effector lymphocytes then mount a cytotoxic response against tumor cells expressing these antigens (see [Related Policies](#) for dendritic cell-based immunotherapy for prostate cancer).

In an attempt to regulate the host immune system further, recent protocols have used various cytokines (eg, IL-7 and IL-15 instead of interleukin -2) to propagate lymphocytes. Protocols also



differ in the extent of host lymphodepletion induced prior to transfusing lymphocytes to the tumor-bearing host.

Note: Allogeneic cell transplantation following nonmyeloablative conditioning of the recipient (known as reduced-intensity conditioning) also may be referred to as “adoptive immunotherapy” in the literature. However, reduced-intensity conditioning cell transplantation relies on a donor-versus-malignancy effect of donor lymphocytes. In contrast, the adoptive immunotherapy techniques described in this policy enhance autoimmune effects primarily. The use of reduced-intensity conditioning in cell transplantation is discussed for specific cancers in individual policies related to cell transplantation.

Tisagenlecleucel

Tisagenlecleucel is an adoptive immunotherapy in which the T cells of a patient are modified by genetic engineering using a lentiviral vector. The resulting genetic modified cells express a CD-19-directed chimeric antigen receptor protein that consists of an extracellular portion that has a murine anti-CD19 single-chain antibody fragment as well as an intracellular portion that contains T-cell signaling and co-stimulatory domains. Once injected, the genetically modified T cells selectively target and bind to CD19 antigen expressed on the surface of B cells and tumors derived from B cells. Subsequently, the intracellular signaling domains play crucial roles in T-cell activation, persistence, and effector functions.¹⁷

Axicabtagene Ciloleucel

Similar to tisagenlecleucel, axicabtagene ciloleucel is an adoptive immunotherapy in which the T cells of a patient are modified genetically using a retroviral vector. The resulting genetically modified cells express a CD-19-directed chimeric antigen receptor protein that has a murine single-chain variable fragment with specificity for CD19. Once injected, the genetically modified T cells selectively target and bind to CD19 antigen expressed on the surface of normal and malignant B cells.¹⁸



Summary of Evidence

Cytotoxic T Lymphocytes

For individuals with Epstein-Barr virus (EBV)-associated cancers who receive cytotoxic T lymphocytes (CTL), the evidence includes two small, prospective noncomparative cohort studies. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The cohort studies have shown a treatment response to infused cytotoxic T lymphocytes directed against cancer-associated viral antigens. To establish efficacy, the following are needed: large, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with Cytomegalovirus-associated cancers who receive CTL, the evidence includes a single case series. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. In the absence of an RCT comparing CTL with the standard of care, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Cytotoxic-Induced Killer Cells

For individuals with nasopharyngeal carcinoma who receive CIK cells, the evidence includes a single RCT. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCT reported a numerically favorable but statistically insignificant effect on progression-free survival and overall survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with renal cell carcinoma (RCC) who receive CIK cells, the evidence includes multiple RCTs. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The largest of the RCTs reported statistically significant gains in progression-free survival and overall survival with CIK cell-based



immunotherapy compared with interleukin-2 plus interferon- α -2. This body of evidence is limited by the context of the studies (non-U.S.) and choice of a nonstandard comparator. The other two RCTs have also reported response rates in favor of CIK therapy with inconsistent effect on survival. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with gastric cancer who receive CIK cells, the evidence includes a single nonrandomized prospective study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The prospective cohort study reported statistically significant effects on disease-free survival and overall survival in favor of immunotherapy vs no immunotherapy. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with colorectal cancer who receive CIK cells, the evidence includes a single RCT and one cohort study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Results of the RCT showed a statistically significant effect on overall survival in favor of immunotherapy vs chemotherapy alone. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with hepatocellular carcinoma who receive CIK cells, the evidence includes several RCTs. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Several RCTs from Asia have generally reported some benefits in response rates and/or survival. The results of a meta-analysis of these trials have also shown a statistically significant 41% reduction in the hazard of death, but there was considerable heterogeneity across the included studies. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.



For individuals with non-small-cell lung cancer (NSCLC) who receive CIK cells, the evidence includes multiple RCTs and a systematic review. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A single systematic review of RCTs reported some benefits in median time to progression and median survival time. The trials assessed in the systematic review were limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Tumor-Infiltrating Lymphocytes

For individuals with melanoma who receive tumor-infiltrating lymphocytes (TIL), the evidence includes a single RCT. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Results of a small RCT have reported no difference in relapse or survival outcomes. Cohort studies in patients with refractory metastatic melanoma have demonstrated response rates of 49% with immunotherapy and 52% to 72% with no immunotherapy. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Dendritic Cells

For individuals with glioblastoma multiforme who receive dendritic cells (DC), the evidence includes a systematic review of observational studies. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Because of the observational and noncomparative nature of the available evidence, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. Interim results from one such RCT have been published but are not informative because the patients were unblinded and results combined for the treatment and



placebo arms. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with non-small-cell lung cancer who receive dendritic cells, the evidence includes two RCTs and a meta-analysis. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The RCTs have generally reported some benefits in response rates and/or survival. The meta-analysis of these trials also reported a statistically significant reduction in the hazard of death. Most trials were from Asia and did not use standard of care as the control arm. This body of evidence is limited by the context of the studies (non-U.S.), small sample sizes, heterogeneous treatment groups, and other methodologic weaknesses. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with medullary thyroid cancer who receive dendritic cells, the evidence includes one prospective noncomparative study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A small prospective noncomparative study in ten medullary thyroid cancer patients treated with autologous dendritic cells has been published. There are no RCTs comparing dendritic cell-based adoptive immunotherapy with standard of care and, therefore, no conclusions can be made. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with pancreatic cancer who receive dendritic cells, the evidence includes a small prospective noncomparative study. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The study reported on treatment outcomes for five patients with pancreatic cancer. Because of the noncomparative nature of the available evidence and small sample base, it is difficult to draw any meaningful conclusions. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.



Genetically Engineered T Cells

Peripheral T Lymphocytes

For individuals with cancers who receive autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors, the evidence includes multiple small observational studies. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. Multiple observational studies have examined autologous peripheral T lymphocytes containing tumor antigen-specific T-cell receptors in melanoma, Hodgkin and non-Hodgkin lymphoma, prostate tumors, and neuroblastoma. Because of the noncomparative nature of the available evidence and a small sample size, it is difficult to draw any meaningful conclusion. To establish efficacy, the following are needed: larger, well-conducted, multicentric trials with adequate randomization procedures, blinded assessments, centralized oversight, and the use of an appropriate standard of care as the control arm showing treatment benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Tisagenlecleucel

For individuals who are up to 25 years of age with relapsed or refractory B-cell acute lymphoblastic leukemia who receive tisagenlecleucel, the evidence includes multiple single-arm prospective trials. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trials reported an 83% response rate (measured by complete response or complete remission with incomplete blood count) in heavily pretreated patients. All patients who achieved a complete remission or complete remission with incomplete blood count were also minimal residual disease–negative, which is predictive of survival in acute lymphoblastic leukemia patients. After a median follow-up of 4.8 months, the median duration of response was not reached. The observed benefits seen with tisagenlecleucel were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (63%) of the patients, and approximately 40% had an adverse event at grade 4 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are adults with a histologically confirmed diagnosis of aggressive non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma, transformed follicular lymphoma) who receive tisagenlecleucel, the evidence



includes a single-arm prospective trial. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 50% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 9.4 months, the median duration of response was not reached. The observed benefits were offset by a high frequency and severity of adverse events. Any grade cytokine release syndrome was observed in 74% of the patients, and 23% had grade 3 or higher cytokine release syndrome. Long-term follow-up and real-world evidence are required to assess the generalizability of tisagenlecleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Axicabtagene Ciloleucel

For individuals who are adults with a histologically confirmed diagnosis of aggressive non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma) who receive axicabtagene ciloleucel, the evidence includes a single-arm prospective trial. The relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 72% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 7.9 months, the median duration of response was 9.2 months. The observed benefits were offset by a high frequency and severity of adverse events. Cytokine release syndrome was observed in more than half (63%) of the patients, and 44% had an adverse event at grade 3 or higher. Long-term follow-up and real-world evidence are required to assess the generalizability of axicabtagene ciloleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some trials that might influence this review are listed in [Table 1](#).



Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Cytotoxic induced killer cells			
NCT02118415	Targeted Natural Killer (NK) Cell Based Adoptive Immunotherapy for the Treatment of Patients With Non-Small Cell Lung Cancer (NSCLC) After Radiochemotherapy (RCT)	90	Feb 2018 (ongoing)
NCT02229266	Randomized Controlled Phase-2 Trial to Determine the Efficacy of Adoptive Immunotherapy With NK Cells in High-risk AML (HINKL)	56	Sep 2020
Tumor-infiltrating lymphocytes			
NCT01993719	A Phase II Prospective Randomized Study of Cell Transfer Therapy for Metastatic Melanoma Using Tumor Infiltrating Lymphocytes Plus IL-2 Comparing Two Different Chemotherapy Preparative Regimens	64	Sep 2029
NCT01966289	A Pilot Study of SGI-110 in Combination With an Allogeneic Colon Cancer Cell Vaccine (GVAX) and Cyclophosphamide (CY) in Metastatic Colorectal Cancer (mCRC) as Maintenance Therapy	18	Dec 2019
NCT01319565	Prospective Randomized Study of Cell Therapy for Metastatic Melanoma Using Short-Term Cultured Tumor Infiltrating Lymphocytes Plus IL-2 Following Either a Non-Myeloablative Lymphocyte Depleting Chemotherapy Regimen Alone or in Conjunction w/1200 TBI	102	Jun 2020
NCT02278887	Randomized Phase III Study Comparing a Non-myeloablative Lymphocyte Depleting Regimen of Chemotherapy Followed by Infusion of Tumor Infiltrating Lymphocytes and Interleukin-2 to Standard Ipilimumab Treatment in Metastatic Melanoma	168	Sep 2020
Autologous dendritic cells			
NCT00338377^a	Lymphodepletion Plus Adoptive Cell Transfer With or Without Dendritic Cell Immunization	189	Feb 2019
NCT01204684	A Phase II Clinical Trial Evaluating Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen +/- Toll-like Receptor Agonists for the Treatment of Malignant Glioma	60	Oct 2019
Dendritic cells/cytokine-induced killer cells			
NCT01691625^a	Concurrent Chemoradiation With or Without DC-CIK Immunotherapy in Treating Locally Advanced Esophageal Cancer	50	Sep 2019



NCT No.	Trial Name	Planned Enrollment	Completion Date
Tisagenlecleucel			
NCT02445248	A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)	116	Feb 2023
NCT02228096	A Phase II, Single Arm, Multicenter Trial to Determine the Efficacy and Safety of CTL019 in Adult Patients With Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)	64	Dec 2022
NCT02445222	Long Term Follow-Up of Patients Exposed to Lentiviral-Based CD19 Directed CAR T-Cell Therapy	620	May 2035
Axicabtagene ciloleucel			
NCT02601313	A Phase 2 Multicenter Study Evaluating Subjects With Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)	130	Mar 2035
NCT02614066	A Study Evaluating KTE-C19 in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3) (ZUMA-3)	100	Mar 2034
NCT02625480	A Multi-Center Study Evaluating KTE-C19 in Pediatric and Adolescent Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (ZUMA-4)	100	Oct 2034
NCT03105336	A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5)	80	Mar 2034

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

Current guidelines from the National Comprehensive Cancer Network do not include recommendations for adoptive immunotherapy to treat cancers of the bladder,⁷⁴ central nervous system,⁷⁵ head and neck,⁷⁶ hepatobiliary system,⁷⁷ kidney,⁷⁸ pancreatic,⁷⁹ stomach,⁸⁰ thyroid,⁸¹⁹ melanoma,⁸² Hodgkin lymphoma,⁸³ or non-small-cell lung cancer.⁸⁴

Current National Comprehensive Cancer Network guidelines for acute lymphoblastic leukemia recommend (category 2A) tisagenlecleucel as a treatment option for⁸⁵:

- 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.

Current Network guidelines for B-cell lymphomas recommend (category 2A) axicabtagene ciloleucel or tisagenlecleucel as a treatment option⁸⁶

- For histological transformation to diffuse large B-cell lymphoma after multiple lines of prior therapies which include ≥ 2 chemo-immunotherapy regimens for indolent or transformed disease.
- For relapsed or refractory disease diffuse large B-cell lymphoma after multiple lines of prior therapies which include ≥ 2 chemo-immunotherapy regimens for indolent or transformed disease.

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

On August 30, 2017, tisagenlecleucel (Kymriah™; Novartis) 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 October 18, 2017, axicabtagene ciloleucel (Yescarta™; Kite Pharma) 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, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

On May 1, 2018, tisagenlecleucel (Kymriah™; Novartis) 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 DLBCL arising from follicular lymphoma.

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History

Date	Comments
01/97	Add to Therapy Section - New Policy
05/19/98	Replace policy. Policy updated; new indications
12/10/02	Replace policy. Policy updated; new references added. No change in policy statement.
04/15/03	Replace policy. Policy reviewed with CPT codes added. No change in policy statement.
01/01/04	Replace policy. CPT code updates only.
05/11/04	Replace policy. Policy updated; no change in policy statement. Additional discussion of dendritic cell therapy.
06/14/05	Replace policy. Policy updated with literature search; no change in policy statement.
02/06/06	Codes Updated. No other changes.
06/16/06	Replace policy. Policy updated with literature search; no change in policy statement;



Date	Comments
	Scope and Disclaimer updated.
06/12/07	Replace policy. Policy updated; no change in policy statement. Reviewed and recommended by OAP on May 24, 2007.
01/13/09	Replace policy. Policy updated with literature search. Policy statement updated to include "adoptive cellular therapy (ACT) for the administration of lymphokine-activated killer cells (LAK) tumor-infiltrating lymphocytes (TIL), or antigen-loaded dendritic cells (ADCs)" as an investigational indication. Investigational statement deleted. References added. Reviewed and recommended by OAP on August 21, 2008.
12/08/09	Cross Reference Update - No other changes.
05/11/10	Cross Reference Update - No other changes.
06/13/11	Replace policy. Policy updated with literature search; reference numbers 33–48 added; no change in policy statements. ICD-10 codes added to policy.
02/14/12	Replace policy. Policy updated with literature search; references 23 and 24 added and other references renumbered or removed. No change in policy statements.
08/15/12	Update Related Policies: remove 2.03.04, as it was archived.
09/28/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
02/13/13	Replace policy. Policy updated with literature search; Two systematic reviews added; Primary studies added on cytokine-induced killer (CIK) cells; references 1, 3-6, 24, and 27 added and other references renumbered. The wording of the policy statement under adoptive cellular therapy was changed to include cytokine-induced killer (CIK) cells; however, the intent of both policy statements (i.e., investigational) is unchanged. Remove Related Policy 2.03.500 as it was archived.
07/25/13	Update Related Policies. Add 8.01.520.
02/24/14	Replace policy. Policy updated with literature search through November 8, 2013; references 3, 8, 27, and 31 added. No change in policy statements.
02/25/15	Annual Review. Policy updated with literature review through November 2, 2014; references 6-9, 12, 14-17, 41, 46, 52-53, and 56-65 added; reference 55 updated. Rationale reorganized and references renumbered. Cytotoxic T-lymphocytes and genetically engineered T cells added to investigational policy statements; "autologous" added to clarify antigen-loaded dendritic cells. ICD-9 and ICD-10 codes removed; these are not utilized in policy adjudication.
02/09/16	Annual Review. Policy updated with literature review through November 10, 2015; references 13 and 17-18 added. Section on lymphokine-activated killer cell deleted as this is an obsolete intervention. Policy statements unchanged.
01/01/18	Annual Review, approved December 12, 2017. Policy updated with literature review through April 2017. Policy statement changed for clarity as Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel) are addressed in policy 5.01.580. Removed codes 96365, 96367, 96368, and S2107.



Date	Comments
11/01/18	Annual Review, approved October 19, 2018. Policy criteria for Chimeric Antigen Receptor (CAR) T Cell Therapies is now addressed in this policy; added codes J3590, Q2040, Q2041, S2107. Removed CPT code 37799. Policy 5.01.580 is now deleted. Policy updated with literature review through June 2018; several references added.
11/17/18	Minor update, added Documentation Requirements section.
01/01/19	Coding update, added 0537T, 0538T, 0539T, 0540T, and Q2042 (new codes effective 1/1/19).
04/01/19	Annual Review, approved March 19, 2019. Policy updated with literature review through October 2018; reference 31 added. Policy statements unchanged.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.



Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
 - Qualified sign language interpreters
 - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
 - Qualified interpreters
 - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with: Civil Rights Coordinator - Complaints and Appeals PO Box 91102, Seattle, WA 98111 Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357 Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services 200 Independence Avenue SW, Room 509F, HHH Building Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD) Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማርኛ (Amharic):

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀናት ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለማመልከት በአስፈላጊ እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):

يحتوي هذا الإشعار على معلومات هامة. قد يحتوي هذا الإشعار على معلومات مهمة بخصوص طلبك أو التخطيط التي تزيد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تاريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):

Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):

Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):

Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnu ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyuog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenna coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyto wenna tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):

この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):

ແຈ້ງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈໍາເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວີ້ ຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកកាមរយ: Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កំណត់ថ្លៃជាតំបន់នានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងអន្តរជាតិរបស់អ្នក ឬប្រាក់ដុល្លារចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងដុល្លារនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਰਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilu fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).