MEDICAL POLICY – 8.01.01
Adoptive Immunotherapy

BCBSA Ref. Policy: 8.01.01

Effective Date: Jan. 1, 2018
Last Revised: Dec. 12, 2017
Replaces: N/A

RELATED MEDICAL POLICIES:
5.01.580 Chimeric Antigen Receptor (CAR) T Cell Therapies
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.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

The immune system is made up of a number of 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 treatment 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 In this technique certain types of immune system cells are withdrawn from the person to be treated.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 attack and defeat cancer cells. This is an active area of study. Because the medical research is not yet complete, many types of adoptive immunotherapy are considered investigational.

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
Adoptive immunotherapy, using adoptive cellular therapy

Kymriah™ (tisagenlecleucel) and Yescarta™ (axicabtagene ciloleucel) are addressed in a separate medical policy (see policy 5.01.580).

All other adoptive immunotherapies (not addressed in separate medical policies), using adoptive cellular therapy for the administration of cytotoxic T lymphocytes, cytokine-induced killer cells, tumor-infiltrating lymphocytes, antigen-loaded autologous dendritic cells, or genetically engineered T cells are considered investigational.

Other applications

Other applications of adoptive immunotherapy are considered investigational.

Coding

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<td>36511</td>
<td>Therapeutic apheresis; for white blood cells</td>
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<td>37799</td>
<td>Unlisted procedure, vascular surgery (therapeutic leukopheresis)</td>
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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 apheresis procedure or may be isolated from resected tumor tissue.

Evidence Review
Description

The spontaneous regression of certain cancers (e.g., 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

Adoptive Immunotherapy

Adoptive immunotherapy uses “activated” lymphocytes as a treatment modality. Both nonspecific and specific lymphocyte activation are used therapeutically. Non-specific, polyclonal proliferation of lymphocytes by cytokines (immune system growth factors), called autolymphocyte 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 that have been pulsed with tumor antigens. Alternatively, innate tumor-infiltrating lymphocytes (TIL) from the tumor biopsy are propagated in vitro with IL-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.¹
**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 (ACT) and antigen-loaded dendritic cell infusions.

ACT is "the administration of a patient's own (autologous) or donor (allogeneic) anti-tumor lymphocytes following a lymphodepleting preparative regimen."² 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 (ELISA)
4. Lymphodepletion of the host with immunosuppressive agents
5. Adoptive transfer (ie, transfusion) of lymphocytes back into the tumor-bearing host

Dendritic cell-based immunotherapy uses autologous dendritic cells (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⁺ T cells, CD8⁺ 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. (Note: See medical policy 8.01.53 for dendritic cell-based immunotherapy for prostate cancer.)

In an attempt to further regulate the host immune system, recent protocols use various cytokines (eg, IL-7 and IL-15 instead of IL-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 [RIC]) also may be referred to as “adoptive immunotherapy” in the literature. However, RIC -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 RIC in cell
transplantation is discussed for specific cancers in individual policies related to stem-cell transplantation.

Summary of Evidence

**Cytotoxic T Lymphocytes**

For individuals with Epstein-Barr virus-associated cancers who receive cytotoxic T lymphocytes, the evidence includes 2 small, prospective noncomparative cohort studies. 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 is 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 cytotoxic T lymphocytes, the evidence includes a single case series. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. In the absence of an RCT comparing cytotoxic T lymphocytes with standard of care, no conclusions can be made. To establish efficacy, the following is 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. 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 is 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 who receive CIK cells, the evidence includes multiple RCTs. 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 2 RCTs have also reported response rates in favor of CIK therapy with inconsistent effect on survival. To establish efficacy, the following is 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. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The prospective cohort study reported statistically significant effect on disease-free survival and overall survival in favor of immunotherapy vs no immunotherapy. To establish efficacy, the following is 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. 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 is 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. 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 is 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 who receive CIK cells, the evidence includes multiple RCTs and a systematic review. 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 included body of evidence trials in the systematic review 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 is 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, the evidence includes a single RCT. 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 is 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, the evidence includes a systematic review of observational studies. 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 is 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 who receive dendritic cells, the evidence includes 2 RCTs and a meta-analysis. 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 results of a meta-analysis of these trials also reported a statistical 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 is 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. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. A small prospective noncomparative study in 10 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 is 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. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The study reported on treatment outcomes for 5 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 is 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. 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, prostate tumors, and neuroblastoma. Because of the noncomparative nature of the available evidence with a small sample size, it is difficult to draw any meaningful conclusion. To establish efficacy, the following is 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.

**Ongoing and Unpublished Clinical Trials**

Some trials that might influence this review are listed in **Table 1**.

**Table 1. Summary of Key Trials**

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<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Cytotoxic T lymphocytes</strong></td>
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<td>NCT02227641</td>
<td>Preventive/Preemptive Adoptive Transfer of Peptide Stimulated CMV/EBV Specific T-cells in Patients After Allogeneic Stem Cell Transplantation</td>
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<td><strong>Lymphokine-activated killer cells</strong></td>
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<td>NCT02118415</td>
<td>Targeted Natural Killer (NK) Cell Based Adoptive Immunotherapy for the Treatment of Patients With Non-Small Cell Lung Cancer (NSCLC) After Radiochemotherapy (RCT)</td>
<td>90</td>
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<tr>
<td>NCT02229266</td>
<td>Randomized Controlled Phase-2 Trial to Determine the Efficacy of Adoptive Immunotherapy With NK Cells in High-risk AML (HINKL)</td>
<td>56</td>
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<tr>
<td><strong>Tumor-infiltrating lymphocytes</strong></td>
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<td></td>
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<tr>
<td>NCT01319565</td>
<td>Prospective Randomized Study of Cell Therapy for</td>
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<td>Jun 2020</td>
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<td>NCT No.</td>
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<td>NCT01966289</td>
<td>SGI-110 in Combination With an Allogeneic Colon Cancer Cell Vaccine (GVAX) and Cyclophosphamide (CY) in Metastatic Colorectal Cancer (mCRC)</td>
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<td>NCT01993719</td>
<td>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</td>
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<td>NCT01995344</td>
<td>TIL Therapy in Metastatic Melanoma and IL2 Dose Assessment (METILDA)</td>
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<tr>
<td>NCT02278887</td>
<td>Study Comparing TIL to Standard Ipilimumab in Patients With Metastatic Melanoma (TIL)</td>
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**Autologous dendritic cells**

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<td>NCT00045968a</td>
<td>Study of a Drug [DCVax®-L] to Treat Newly Diagnosed GBM Brain Cancer</td>
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<td>NCT00338377a</td>
<td>Lymphodepletion Plus Adoptive Cell Transfer With or Without Dendritic Cell Immunization</td>
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<tr>
<td>NCT01204684</td>
<td>Dendritic Cell Vaccine for Patients With Brain Tumors</td>
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**Dendritic cells/cytokine-induced killer cells**

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<td>NCT01691625a</td>
<td>Concurrent Chemoradiation With or Without DC-CIK Immunotherapy in Treating Locally Advanced Esophageal Cancer</td>
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<tr>
<td>NCT02202928</td>
<td>Adoptive Cell Therapy Plus Chemotherapy and Radiation After Surgery in Treating Patients With Colorectal Cancer</td>
<td>60</td>
<td>Dec 2017</td>
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</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

**Practice Guidelines and Position Statements**

Current guidelines from the National Comprehensive Cancer Network (NCCN) do not include recommendations for adoptive immunotherapy to treat cancers of the bladder,59 central nervous
system, head and neck, hepatobiliary system, kidney, pancreas, stomach, thyroid, melanoma, Hodgkin lymphoma, or non-small-cell lung cancer.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

Adaptive immunotherapy is not a U.S. Food and Drug Administration–regulated procedure.

References


### History

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<td>Replace policy. Policy updated with literature search. Policy statement updated to included “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.</td>
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<td>Update Related Policies: remove 2.03.04, as it was archived.</td>
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<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
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<td>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.</td>
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<td>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.</td>
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Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen enfômasyon enpòtad laidann. Avi sila a kapab genyen enfômasyon enpòtan konsénan aplikasyon w lan oswa konsénan kvoutè ki asirans lan atravé Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka jebo kvoutè ki asirans sante w lan oswa pou yo ka ede w avèk depans yo. Se dw a pou reseswa enfômasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Iloklo (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalini nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonwyo wens coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a petsa iti daytoy a pakdaar. Mabalini nga adda rumbeng a aramidenyo nga addang sakbay dagiti partikular a naituding nga aildaw tapno mapagtaiine dyo coverage ti salun-ayyo wens tulong kadagit gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

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，以便獲得您的健康保險或費用補貼。如有困難免費以您的母語得到本訊息和幫助。請接電話 800-722-1471 (TTY: 800-842-5357).

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Premera Blue Cross (TTY: 800-842-5357).