Clinical Policy Title: Immune cell function assay

Clinical Policy Number: CCP.1363

Effective Date: April 1, 2018
Initial Review Date: February 6, 2018
Most Recent Review Date: March 5, 2019
Next Review Date: March 2020

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of immune cell function assays (e.g., ImmuKnow® [Cylex, Inc. now manufactured by Viracor Eurofins Inc., Lee’s Summit, Missouri] or Pleximmune® [Plexision Inc., Pittsburgh, Pennsylvania]) to be investigational and, therefore, not medically necessary.

Limitations:
Not applicable.

Alternative covered services:

Standard of care for patient evaluation and management by a network health care provider.

Background
Cellular immune function is an important factor in risk for acute graft rejection, opportunistic infection, and cancer among immunosuppressed transplant recipients (Bestard, 2017). Immune status monitoring is necessary to balance the risk of immunosuppressant therapy and drug-related toxicity. The most frequently used tools to monitor immunosuppression in transplant recipients are therapeutic drug levels in the blood, antihuman leukocyte antigen antibody assays, and the presence of opportunistic infections, but they are often insufficient to differentiate rejection from toxicity, necessitating allograft biopsy.

Immune cell function assays are biomarkers that quantify T-cell and B-cell alloreactivity noninvasively, some of which may also provide important information in the management of autoimmune diseases (Bestard, 2017). These tests may address an unmet need for a safer, more tolerable, and cost-effective approach to immunosuppression.

Pleximmune:

Pleximmune is a qualitative prognostic test that measures the inflammatory response of T-cytotoxic memory lymphocytes to donor cells and reports the results as a numeric score called the immunoreactivity index (Plexision, 2017). The index is compared with a rejection-risk threshold developed from testing of over 200 liver or intestine recipients to assign risk. The U.S. Food and Drug Administration (2014) approved Pleximmune under a Humanitarian Device Exemption for prediction of acute cellular rejection within 60 days after transplantation in patients less than 21 years old with liver or intestine transplantation. It is intended to be used in the pre-, early-, and late-transplantation periods in conjunction with biopsy, standard clinical assessment, and other laboratory information.

ImmuKnow:

ImmuKnow measures the adenosine triphosphate response of stimulated peripheral blood lymphocytes (CD4+ T-cells) as an index of lymphocyte activity. The measurement of CD4 activation reflects the degree of immune function. The U.S. Food and Drug Administration (2002) issued 510(k) approval for detection of cell-mediated immunity in organ transplant recipients receiving immunosuppressive therapy.

Searches

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.
- The Cochrane Library.

We conducted searches on February 5, 2019. Search terms were: “immunocompetence” (MeSH), “cellular, immunity” (MeSH), “ImmuKnow,” “Pleximmune,” and “immune reactive capacity.”
We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

One study evaluated the diagnostic accuracy of the Pleximmune test (Sindhi, 2016). The sensitivity and specificity of Pleximmune for predicting acute cellular rejection were 0.84 and 0.80, respectively, in training set-validation set testing of 214 children (Sindhi, 2016).

Three meta-analyses examined the diagnostic performance of ImmuKnow for predicting infection and acute rejection after kidney transplantation (Wang, 2014), liver transplantation (Rodrigo, 2012), and a mixed transplant population (Ling, 2012). The evidence consists of retrospective, cross-sectional studies. The results from these studies suggest associations between the assay results and presence of clinically relevant post-transplantation outcomes, but data from prospective studies are needed to clarify these associations. The overall findings do not support ImmuKnow as a diagnostic or predictive test for use in monitoring immune status in transplantation recipients.

A meta-analysis (Wang, 2014) of six studies determined that, for predicting infection, ImmuKnow had a sensitivity of 0.51, specificity of 0.75, a positive likelihood ratio\(^1\) of 1.97, a negative likelihood ratio of 0.67, and a diagnostic odds ratio\(^2\) of 3.56. For predicting acute rejection, the results were sensitivity of 0.51, specificity of 0.90, a positive likelihood ratio of 4.45, a negative likelihood ratio of 0.35, and a diagnostic odds ratio of 13.81. The authors concluded that the data did not support the use of the ImmuKnow assay to predict or monitor the risks of infection and acute rejection in renal transplant recipients.

A meta-analysis (Rodrigo, 2012) assessed ImmuKnow as a diagnostic tool for predicting infection (five studies) and acute rejection (five studies) in adults after liver transplantation. For predicting infection, ImmuKnow demonstrated a sensitivity of 0.84 and a specificity of 0.75. According to the diagnostic odds

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\(^1\) Likelihood ratios determine whether a test result usefully changes the probability that a disease state exists. A likelihood ratio close to 1 means the test result does not change the likelihood of disease or the outcome of interest appreciably (Simundic, 2009).

\(^2\) A diagnostic odds ratio assesses the test’s discriminatory capacity among healthy and sick, i.e., odds of expected test result (positivity) in subjects with disease relative to the odds in subjects without disease. Values range from zero to infinity (Simundic, 2009).
ratio, transplant recipients with a positive ImmuKnow result had 14.6 greater odds of having an infection than patients with a negative test result, and a positive likelihood ratio of 3.3 suggests that a positive ImmuKnow result increases the post-test probability of infection. In contrast, ImmuKnow’s test performance for acute rejection could not be validated due to considerable heterogeneity across studies.

A meta-analysis (Ling, 2012) of nine studies in post-transplantation recipients determined that the pooled estimates for identifying infection risk were poor, with a sensitivity of 0.58, a specificity of 0.69, a positive likelihood ratio of 2.37, a negative likelihood ratio of 0.39, and a diagnostic odds ratio of 7.41. The pooled estimates for identifying risk of rejection were also fairly poor with a sensitivity of 0.43, a specificity of 0.75, a positive likelihood ratio of 1.30, a negative likelihood ratio of 0.96, and a diagnostic odds ratio of 1.19.

The American Society of Transplantation does not mention the use of the ImmuKnow immune cell function assay in its recommendations for the screening, monitoring, and reporting of infections and complications in the evaluation of recipients of organ transplantation (Humar, 2006, reaffirmed 2013).

**Policy updates:**

In 2019, we added one randomized controlled trial (Ravaioli, 2015) and two evidence-based guidelines (Green, 2013; Lucey, 2013) to the policy. Compared with current monitoring practices (n = 102), Ravaioli et al. found immunosuppression modifications based on serial ImmuKnow measurement (n = 100) was associated with improved 1-year patient survival (95 percent versus 82 percent, \( P < .01 \)) and a lower incidence of infections longer than 14 days after transplantation (42 percent versus 55 percent, \( P < .05 \)).

Professional guidelines from the American Transplantation Society (Green, 2013) and a joint guideline by the American Transplantation Society and the American Association for the Study of Liver Diseases (Lucey, 2013) noted the multifactorial challenges in quantifying the degree of immunosuppression in an individual organ recipient. Neither mentioned the role of immune cell function assays in the post-transplantation recipient. The clinical role of ImmuKnow remains undetermined, as it is unlikely that an immune cell function assay alone will provide sufficient information to characterize the complex pathophysiology of an individual's alloreactivity. No policy changes are warranted. The policy ID was changed from CP# 02.02.26 to CCP.1363.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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