**Medical Coverage Policy |** Immune Cell Function Assay

**EFFECTIVE DATE:** 10|01|2015
**POLICY LAST UPDATED:** 10|02|2018

## OVERVIEW
This policy documents the coverage determination for use of immune cell function assays. Careful monitoring of lifelong immunosuppression is required to ensure long-term viability of solid organ allografts without incurring an increased risk of infection. The monitoring of immunosuppression parameters attempts to balance the dual risks of rejection and infection. It is proposed that individual immune profiles, such as an immune cell function assay, will help assess the immune function of the transplant recipient and individualize immunosuppressive therapy.

## MEDICAL CRITERIA
Not applicable

## PRIOR AUTHORIZATION
Not applicable

## POLICY STATEMENT
**BlueCHiP for Medicare**
Use of the immune cell function assay to monitor and predict immune function after solid organ transplantation, hematopoietic stem-cell transplantation, and all other indications is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

**Commercial Products**
Use of the immune cell function assay to monitor and predict immune function after solid organ transplantation, hematopoietic stem-cell transplantation, and all other indications is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

## COVERAGE
Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

## BACKGROUND
In current clinical practice, levels of immunosuppression in patients being managed after solid organ transplant or hematopoietic cell transplantation (HCT) and determined by testing for clinical toxicity (eg, leukopenia, renal failure) and by therapeutic drug monitoring when available. However, drug levels are not a surrogate for overall drug distribution or efficacy because pharmacokinetics often differ among individuals due to clinical factors such as underlying diagnosis, age, sex, and race; circulating drug levels may not reflect the drug concentration in relevant tissues; and serum level of an individual immunosuppressant drug may not reflect the cumulative effect of other concomitant immunosuppressants. The main value of therapeutic drug monitoring is the avoidance of toxic. Individual immune profiles, such as an immune cell function assay, could support clinical decision making and help to manage the risk of infection from excessive immunosuppression and the risk of rejection from inadequate immunosuppression. Several commercially available tests of immune cell function have been developed to support clinical decision making.

ImmuKnow measures the concentration of adenosine triphosphate (ATP) in whole blood after a 15- to 18-hour incubation with phytohemagglutinin (a mitogenic stimulant). Cells that respond to stimulation show

increased ATP synthesis during incubation. Concurrently, whole blood is incubated in the absence of stimulant for the purpose of assessing basal ATP activity. CD4 positive T lymphocytes are immunoselected from both samples using anti-CD4 monoclonal antibody-coated magnetic particles. After washing the selected CD4 positive cells on a magnet tray, a lysis reagent is added to release intracellular ATP. A luminescence reagent added to the released ATP produces light measured by a luminometer, which is proportional to the concentration of ATP. The characterization of the cellular immune response of a specimen is made by comparing the ATP concentration for that specimen with fixed ATP production ranges.

Pleximmune™ measures CD154 expression on T-cytotoxic memory cells in patient's peripheral blood lymphocytes. CD154 is a marker of inflammatory response. To characterize risk of rejection, the patient's inflammatory response to (transplant) donor cells is expressed as a fraction of the patient's inflammatory response to third-party cells. This fraction or ratio is called the Immunoreactivity Index (IR). If the donor-induced response exceeds the response to third-party cells, the individual is at increased risk for rejection. Cells are cultured and then analyzed with fluorochrome-stained antibodies to identify the cells expressing CD154. For posttransplant blood samples, an IR greater than 1.1 indicates increased risk of rejection, and an IR less than 1.1 indicates decreased risk of rejection. For pretransplant samples, the threshold for IR is 1.23.

Regulatory Status

In April 2002, ImmuKnow® (Cylex, acquired by ViraCor-IBT Laboratories, Lee's Summit, MO), an immune cell function assay, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA-indicated use of ImmuKnow® is for the detection of cell-mediated immune response in populations undergoing immunosuppressive therapy for organ transplant.

In April 2002, Immune Cell Function Assay (Cylex) was cleared for marketing by FDA through the 510(k) process. The FDA-indicated use of the Immune Cell Function Assay is for the detection of cell-mediated immune response in an immunosuppressed population. In 2010, a device modification for this assay was cleared for marketing by FDA through the 510(k). There were no changes to the indications or intended use.

In August 2014, Pleximmune™ (Plexision) was approved by FDA through the humanitarian device exemption process. The test is intended for use in the pretransplantation and early and late posttransplantation period in pediatric liver and small bowel transplant patients for the purpose of predicting the risk of transplant rejection within 60 days after transplantation or 60 days after sampling.

For individuals who have a solid organ transplant or hematopoietic cell transplant (HCT) who receive testing using an immune cell function assay with ImmuKnow, the evidence includes numerous studies on the association of assay test values and subsequent rejection or infection, and a randomized controlled trial in liver transplant patients. Relevant outcomes are overall survival, test accuracy, other test performance measures, and morbid events. The ImmuKnow test has shown variable associations with infection and rejection, depending on the type of transplant and context of the study. Across all the studies among various types of patients, ImmuKnow levels are associated with the risk of rejection when levels are high and risk of infection when levels are low. However, the absolute risk and increments of risk are uncertain because of heterogeneity of the studies. The predictive characteristics of the test are still uncertain, and do not allow a strong chain of evidence for clinical utility. The trial of the ImmuKnow test in liver transplant patients showed improvement in overall survival; however, the trial had several limitations. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a solid organ transplant or hematopoietic cell transplant who receive testing using an immune cell function assay with Pleximmune, the evidence includes the U.S. Food and Drug Administration documentation and a report on the test's development and validation. Relevant outcomes are overall survival, test accuracy, other measures of test performance, and morbid events. Small studies have

shown that Pleximmune values correlate with long-term survival. Pleximmune test results correlated with rejection, but conclusions are uncertain because of extremely limited evidence deriving from a small number of patients described briefly in approval documents and a second study, in which the confidence interval bounds for sensitivity and specificity estimates were wide. No direct studies of clinical utility were identified. An argument for clinical utility using a chain of evidence would rely on both a demonstration of clinical validity and a rationale that specific clinical interventions based the results of the test decrease the risk of a poor health outcome. At present, the clinical interventions that would occur as a result of the test result are uncertain, and so the clinical validity is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

## CODING

The following service is not covered for BlueCHiP for Medicare and considered not medically necessary for Commercial products:

**86352** Cellular function assay involving stimulation (eg, mitogen or antigen) and detection of biomarker (eg, ATP)

## RELATED POLICIES

None

## PUBLISHED

Provider Update, Nov. /Dec. 2018
Provider Update, October 2017
Provider Update, January 2017
Provider Update, August 2015

## REFERENCES


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