Medical Coverage Policy | Immune Cell Function Assay

EFFECTIVE DATE: 10|01|2015
POLICY LAST UPDATED: 12|06|2016

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 and 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 there is insufficient peer-reviewed literature that demonstrates that the service is effective.

COVERAGE
Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage, Subscriber Agreement, or Benefit Booklet for limitations of benefits/coverage when services are not medically necessary.

BACKGROUND
Currently, immunosuppression is determined by testing for clinical toxicity (e.g., leukopenia, renal failure) and by therapeutic drug monitoring (TDM) 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 TDM is the avoidance of toxic levels and monitoring patient compliance. Further, the appropriate level of immunosuppression may vary from person to person. 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 in immunosuppressed patients.

ImmuKnow® measures the concentration of ATP in whole blood after a 15- to 18-hour incubation with the mitogenic stimulant, phytohemagglutinin. In cells that respond to stimulation, increased ATP synthesis occurs during incubation. Concurrently, whole blood is incubated in the absence of stimulant for the purpose of assessing basal ATP activity. CD4+ T lymphocytes are immunoselected from both samples using anti-CD4 monoclonal antibody-coated magnetic particles. After washing the selected CD4+ 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 donorinduced 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

ImmuKnow® (Cylex, recently acquired by Viracor-IBT Laboratories Inc., Lee's Summit, MO) is an immune cell function assay cleared for marketing by FDA in April 2002 to detect cell-mediated immunity (CMI) in an immunosuppressed patient population.

In April 2002, Cylex obtained 510(k) clearance from FDA to market the Immune Cell Function Assay based on substantial equivalence to 2 flow cytometry reagents ("predicate devices") manufactured by Becton Dickinson, the TriTestTM CD4 FITC/CD8 PE/CD3 PerCP Reagent and the MultiTestTM CD3 FITC/CD8 PE/CD45 PerCP/CD4 APC Reagent. These reagents are used to determine CD4+ Tlymphocyte counts in immunocompromised patients. The FDA-indicated use of the Immune Cell Function Assay is for the detection of CMI in an immunosuppressed population. A subsequent 510(k) marketing clearance for a device modification was issued by FDA for this assay in 2010. 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.

The evidence for immune cell function assay in patients who have a solid organ transplant includes numerous studies of the association of assay test values and subsequent rejection or infection, and 1 randomized controlled trial in liver transplant patients. Relevant outcomes are overall survival, test accuracy, other test performance measures, and morbid events (rejection and infection). The ImmuKnow® test shows variable associations with infection and rejection depending on the type of transplant and the context of the study. The predictive characteristics of the test are still uncertain, and do not allow a strong indirect argument of clinical utility. The trial of ImmuKnow® in liver transplant patients showed improvement in overall survival; however, the trial has several shortcomings. 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 Food and Drug Administration approval documents. Studies of clinical utility of Pleximmune™ were not identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for immune cell function assay in patients who have a hematopoietic stem cell transplant includes studies correlating ImmuKnow® values with subsequent survival. Relevant outcomes are overall survival, test accuracy, other measures of test performance, and morbid events. Small studies show that ImmuKnow® values correlate with long-term survival. This information on predictive capability could not be linked to improved outcomes. No direct studies of clinical utility were identified. The evidence is insufficient to determine the effects of the technology on health outcomes. Therefore, this service is considered not medically necessary for BlueCHiP for Medicare and Commercial products as there is insufficient peer-reviewed literature that demonstrates that the service is effective.

CODING

BlueCHiP for Medicare and Commercial Products

The following service is considered not medically necessary:

86352

RELATED POLICIES

None

PUBLISHED

Provider Update, January 2017
Provider Update, August 2015

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