



Louisiana

Immune Cell Function Assay

Policy # 00702

Original Effective Date: 06/08/2020

Current Effective Date: 04/12/2021

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Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of the immune cell function assay to monitor and predict immune function after solid organ transplantation to be **investigational**.*

Based on review of available data, the Company considers the use of the immune cell function assay to monitor and predict immune function after hematopoietic cell transplantation to be **investigational**.*

Based on review of available data, the Company considers the use of the immune cell function assay for all other indications to be **investigational**.*

Background/Overview

Immunosuppression for Transplant

In current clinical practice, levels of immunosuppression in patients being managed after a solid organ transplant or hematopoietic cell transplantation are 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 toxicity. 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.

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Treatment

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 stimulants 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 the 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 post transplant blood samples, an IR greater than 1.1 indicates an increased risk of rejection, and an IR less than 1.1 indicates a decreased risk of rejection. For pre transplant samples, the threshold for IR is 1.23.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In April 2002, ImmuKnow^{®†} (Cylex, acquired by ViraCor-IBT Laboratories), an immune cell function assay, was cleared for marketing by the U.S. FDA through the 510(k) process (K013169). The FDA indicated use of ImmuKnow is for the detection of a cell-mediated immune response in populations undergoing immunosuppressive therapy for an organ transplant.

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In April 2002, Immune Cell Function Assay (Cylex) was cleared for marketing by the FDA through the 510(k) process. The FDA indicated use of the Immune Cell Function Assay is for the detection of a 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) (K101911). There were no changes to the indications or intended use.

In August 2014, Pleximmune^{TM‡} (Plexision) was approved by the FDA through the humanitarian device exemption process. The test is intended for use in the pre transplantation and early and late post transplantation 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.

Rationale/Source

Description

Careful monitoring of lifelong immunosuppression is required to ensure the 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.

Summary of Evidence

For individuals who have a solid organ transplant or hematopoietic cell transplant who receive immune cell function assay testing with ImmuKnow, the evidence includes numerous studies on the association between assay test values and subsequent rejection or infection, and a randomized controlled trial in liver transplant patients. Relevant outcomes are overall survival, 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 the 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

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survival; however, the trial had several limitations. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals who have a solid organ transplant or hematopoietic cell transplant who receive immune cell function assay testing with Pleximmune, the evidence includes the U.S. FDA documentation and a report on the test's development and validation. Relevant outcomes are overall survival, 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 the FDA 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 that the technology results in an improvement in the net health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

Transplantation Society

In 2018, the International Cytomegalovirus Consensus Group of the Transplantation Society updated its consensus statement on the management of cytomegalovirus in solid organ transplant. The statement indicated that “there are no clinical studies demonstrating that management decisions based on immunologic monitoring affect patient outcomes.” Routine immunologic monitoring was not recommended.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in October 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

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Policy History

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03/05/2020 Medical Policy Committee review

03/11/2020 Medical Policy Implementation Committee approval. New policy.

03/04/2021 Medical Policy Committee review

03/10/2021 Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 03/2022

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