FEP 2.04.56 Immune Cell Function Assay

**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.

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 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.

**OBJECTIVE**
The objective of this evidence review is to determine whether the use of commercially available assays to assess immune cell function in patients with solid organ transplants and hematopoietic cell transplantation improves the net health outcome.
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POLICY STATEMENT

Use of the immune cell function assay to monitor and predict immune function after solid organ transplantation is considered investigational.

Use of the immune cell function assay to monitor and predict immune function after hematopoietic cell transplantation is considered investigational.

Use of the immune cell function assay for all other indications is considered investigational.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

In April 2002, ImmuKnow® (Cylex, acquired by ViraCor-IBT Laboratories), 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 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

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 survival; however, the trial had several limitations. The evidence is insufficient to determine the effects of the technology on health outcomes.
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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. Food and Drug Administration documentation and a report on the test’s development and validation. Relevant outcomes are overall survival, other measures of test performance, and morbidity 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 Food and Drug Administration 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 on 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Transplantation Society

The International Cytomegalovirus Consensus Group of the Transplantation Society updated its consensus statement on the management of cytomegalovirus in solid organ transplant in 2018. 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

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

REFERENCES


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>June 2012</td>
<td>Update Policy</td>
<td>Policy updated with literature review, two systematic reviews added and summary revised; references reordered; no change in policy statement.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review, adding references 9-11, 13-14, 27-30 and 39-40; references 1 and 42 were updated. There are no changes to the policy statements.</td>
</tr>
<tr>
<td>March 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review through November 10, 2015; references 2 and 33-34 added. References on HIV, lupus nephritis deleted. Policy statements unchanged.</td>
</tr>
<tr>
<td>June 2016</td>
<td>Update Policy</td>
<td>Policy updated with literature review through October 25, 2017; references 28, 29, 37 and 41 added. Policy statements corrected from “not medically necessary” to “investigational” based on FDA 510k and HDE approvals of assay tests.</td>
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March 2019 Update Policy Policy updated with literature review through October 1, 2018; reference 38 added. Policy statements unchanged.