

FEP 2.04.56 Immune Cell Function Assay

Effective Date: April 15, 2018

Related Policies: None

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.

FDA 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 the 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 the FDA through the 510(k). There were no changes to the indications or intended use.¹

In August 2014, Pleximmune™ (Plexision, Pittsburgh, PA) was approved by the FDA through the humanitarian device exemption process.² 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.

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**.

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BENEFIT APPLICATION

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

RATIONALE

Summary of Evidence

For individuals who have a solid organ transplant or hematopoietic cell transplant who receive testing using an immune cell function assay 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, 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 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 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 published a consensus statement on the management of cytomegalovirus in solid organ transplant in 2010.³⁸ 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.

International Society of Heart and Lung Transplantation

Guidelines for the care of heart transplant recipients, published in 2010 by the International Society of Heart and Lung Transplantation, did not include ImmuKnow.³⁹

American Society of Transplantation

In 2006, the American Society of Transplantation published recommendations on the screening, monitoring, and reporting of infectious complications in immunosuppression trials of organ transplant

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recipients.⁴⁰ These recommendations defined relevant infectious complications to be included in the reporting of immunosuppression trials and recommended specific laboratory monitoring and surveillance methods. The immune cell function assay was not included.

Guidelines on Use of Assays for Monitoring Autophagy in Higher Eukaryotes

Guideline updates published in 2016 by Klionsky et al discussed a number of assays in the context of monitoring autophagy, concluding that the best approach would be to use a combination of several assays, as opposed to a single test.⁴¹ The guidelines did not address the topic specific to this evidence review (monitoring of immunosuppression in the context of transplant); they also made no mention of ImmuKnow or Pleximmune in their recommendations.

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.

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POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
June 2012	Update Policy	Policy statement updated to read not medically necessary. References 10, 15-25 added. Previous references renumbered.
March 2013	Update Policy	Policy updated with literature review, two systematic reviews added and summary revised; references reordered; no change in policy statement.
March 2014	Update Policy	Policy updated with literature review, references 14-17 and 19 added; no change in policy statements.
March 2015	Update Policy	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.
June 2016	Update Policy	Policy updated with literature review through November 10, 2015; references 2 and 33-34 added. References on HIV, lupus nephritis deleted. Policy statements unchanged.
March 2018	Update Policy	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.

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