BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.56 Immune Cell Function Assay

Annual Effective Policy Date: April 1, 2024

Original Policy Date: December 2011

Related Policies:

None

Immune Cell Function Assay

Description

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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.

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.

POLICY STATEMENT

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

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

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

POLICY GUIDELINES

None

BENEFIT APPLICATION

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 (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.

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.[1,]

In August 2014, Pleximmune™ (Plexision) 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.

RATIONALE

Summary of Evidence

For individuals with 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 that the technology results in an improvement in the net health outcome.

For individuals with 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 (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 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Transplantation Infectious Diseases Community of Practice

In 2019, the American Society of Transplantation Infectious Diseases Community of Practice updated guidelines on post-transplant lymphoproliferative disorders in solid organ transplant.[41,] A statement indicated: "Simpler rapid assays to measure global and [Epstein-Barr virus] EBV-specific T-cell immunity using commercial ATP release assays (Cyclex ImmuKnow and T-cell Memory) have undergone preliminary evaluation as adjunct markers of [post-transplant lymphoproliferative disorders] PTLD risk when combined with viral load testing in pediatric thoracic transplant recipients but require further validation." Routine immunologic monitoring was not recommended.

Transplantation Society

In 2018,[42,] the International Cytomegalovirus Consensus Group of the Transplantation Society updated its consensus statement on the management of cytomegalovirus in solid organ transplant.[43,] 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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
March 2012	Replace policy	Policy statement updated to read not medically necessary. References 10, 15-25 added. Previous references renumbered.
March 2013	Replace policy	Policy updated with literature review, two systematic reviews added and summary revised; references reordered; no change in policy statement.
March 2014	Replace policy	Policy updated with literature review, references 14-17 and 19 added; no change in policy statements.
March 2015	Replace 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	Replace 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	Replace policy	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 510(k) and HDE approvals of assay tests.
March 2019	Replace policy	Policy updated with literature review through October 1, 2018; reference 38 added. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through October 14, 2019; no references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through October 27, 2020; references added. Policy statements unchanged.
March 2022	Replace policy	Policy updated with literature review through November 5, 2021; references added. Policy statements reworded for clarity but intent of statements unchanged.
March 2023	Replace policy	Policy updated with literature review through September 19, 2022; references added. Policy statements unchanged.
March 2024	Replace policy	Policy updated with literature review through November 17, 2023; no references added. Policy statements unchanged.