BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.56 Immune Cell Function Assay

Annual Effective Policy Date: April 1, 2026

Original Policy Date: December 2011

Related Policies:

None

Immune Cell Function Assay

Description

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.

OBJECTIVE

The objective of this evidence review is to determine whether the use of commercially available assays to assess immune cell function in individuals 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).

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.

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 (HCT) 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 (RCT) in liver transplant patients. Relevant outcomes are overall survival (OS), 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 OS; 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 HCT 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 OS, 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. A third study found lower sensitivity and specificity estimates than previous studies. 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 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.[42,] A statement indicated: "Simpler rapid assays to measure global and [Epstein-Barr virus] EBV-specific T-cell immunity using commercial ATP [adenosine triphosphate] 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.

International Pediatric Transplant Association

In 2024, the International Pediatric Transplant Association (IPTA) published an expert consensus on post-transplant lymphoproliferative disorders after solid organ transplant in children.[43,] A recommendation relevant to this monograph stated: "We do not recommend the use of measurement of ATP release by CD4+ or CD3+ T cells in response to PHA [phytohemagglutinin] or EBV-Ag lysate stimulation (Immuknow Assay) for PTLD related surveillance, diagnosis, or prognosis (weak recommendation, low-quality of evidence)."

Transplantation Society

In 2018,[44,] the International Cytomegalovirus Consensus Group of the Transplantation Society updated its consensus statement on the management of cytomegalovirus in solid organ transplant.[45,]This was updated again most recently in 2025.[46,] They stated that "no studies have shown that routine monitoring of T-cell responses impacts decision making in pediatric transplant recipients...additional work is required on the utility of immunogenetic biomarkers and adjunctive immunologic monitoring to guide treatment strategies. Such work should consider age-related immune maturity issues that might influence the optimal performance of assays."

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.

REFERENCES

1. Food and Drug Administration (FDA). Special 510(k): Device Modification 2010 (K101911). n.d.; http://www.accessdata.fda.gov/cdrh_docs/reviews/K101911.pdf. Accessed October 22, 2025.
2. Food and Drug Administration (FDA). Summary of Safety and Probable Benefit: Pleximmune. 2014; http://www.accessdata.fda.gov/cdrh_docs/pdf13/H130004b.pdf. Accessed October 21, 2025.
3. Ling X, Xiong J, Liang W, et al. Can immune cell function assay identify patients at risk of infection or rejection? A meta-analysis. Transplantation. Apr 15 2012; 93(7): 737-43. PMID 22357178
4. Rodrigo E, Lpez-Hoyos M, Corral M, et al. ImmuKnow as a diagnostic tool for predicting infection and acute rejection in adult liver transplant recipients: a systematic review and meta-analysis. Liver Transpl. Oct 2012; 18(10): 1245-53. PMID 22740321
5. Rossano JW, Denfield SW, Kim JJ, et al. Assessment of the Cylex ImmuKnow cell function assay in pediatric heart transplant patients. J Heart Lung Transplant. Jan 2009; 28(1): 26-31. PMID 19134527
6. Wong MS, Boucek R, Kemna M, et al. Immune cell function assay in pediatric heart transplant recipients. Pediatr Transplant. Aug 2014; 18(5): 485-90. PMID 24930882
7. Ryan CM, Chaudhuri A, Concepcion W, et al. Immune cell function assay does not identify biopsy-proven pediatric renal allograft rejection or infection. Pediatr Transplant. Aug 2014; 18(5): 446-52. PMID 24930482
8. Wozniak LJ, Venick RS, Gordon Burroughs S, et al. Utility of an immune cell function assay to differentiate rejection from infectious enteritis in pediatric intestinal transplant recipients. Clin Transplant. Feb 2014; 28(2): 229-35. PMID 24433466
9. Liu W, Wang K, Zhao YH, et al. Clinical relevance of a CD4 + T cell immune function assay in the diagnosis of infection in pediatric living-donor liver transplantation. Exp Ther Med. Nov 2019; 18(5): 3823-3828. PMID 31602249
10. Xue F, Gao W, Qin T, et al. Immune cell function assays in the diagnosis of infection in pediatric liver transplantation: an open-labeled, two center prospective cohort study. Transl Pediatr. Feb 2021; 10(2): 333-343. PMID 33708519
11. Nishikawa K, Mizuno S, Masui S, et al. Usefulness of monitoring cell-mediated immunity for predicting post-kidney transplantation viral infection. Transplant Proc. 2014; 46(2): 552-5. PMID 24656010
12. Sageshima J, Ciancio G, Chen L, et al. Lack of clinical association and effect of peripheral WBC counts on immune cell function test in kidney transplant recipients with T-cell depleting induction and steroid-sparing maintenance therapy. Transpl Immunol. Mar 2014; 30(2-3): 88-92. PMID 24518158
13. Toro A, Fernndez EJ, Montes-Ares O, et al. Lack of association of immune cell function test with rejection in kidney transplantation. Transplant Proc. 2011; 43(6): 2168-70. PMID 21839223
14. Zhou H, Wu Z, Ma L, et al. Assessing immunologic function through CD4 T-lymphocyte ahenosine triphosphate levels by ImmuKnow assay in Chinese patients following renal transplantation. Transplant Proc. Sep 2011; 43(7): 2574-8. PMID 21911125
15. Huskey J, Gralla J, Wiseman AC. Single time point immune function assay (ImmuKnow) testing does not aid in the prediction of future opportunistic infections or acute rejection. Clin J Am Soc Nephrol. Feb 2011; 6(2): 423-9. PMID 21088287
16. Reinsmoen NL, Cornett KM, Kloehn R, et al. Pretransplant donor-specific and non-specific immune parameters associated with early acute rejection. Transplantation. Feb 15 2008; 85(3): 462-70. PMID 18301338
17. Serban G, Whittaker V, Fan J, et al. Significance of immune cell function monitoring in renal transplantation after Thymoglobulin induction therapy. Hum Immunol. Nov 2009; 70(11): 882-90. PMID 19664673
18. Libri I, Gnappi E, Zanelli P, et al. Trends in immune cell function assay and donor-specific HLA antibodies in kidney transplantation: A 3-year prospective study. Am J Transplant. Dec 2013; 13(12): 3215-22. PMID 24266972

19. Myslik F, House AA, Yanko D, et al. Preoperative Cylex assay predicts rejection risk in patients with kidney transplant. Clin Transplant. May 2014; 28(5): 606-10. PMID 24628326
20. Quaglia M, Cena T, Fenoglio R, et al. Immune function assay (immunknow) drop over first 6 months after renal transplant: a predictor of opportunistic viral infections?. Transplant Proc. Sep 2014; 46(7): 2220-3. PMID 25242755
21. Wang XZ, Jin ZK, Tian XH, et al. Increased intracellular adenosine triphosphate level as an index to predict acute rejection in kidney transplant recipients. Transpl Immunol. Jan 2014; 30(1): 18-23. PMID 24211610
22. Weston MW, Rinde-Hoffman D, Lopez-Cepero M. Monitoring cell-mediated immunity during immunosuppression reduction in heart transplant recipients with severe systemic infections. Clin Transplant. Mar 2020; 34(3): e13809. PMID 32003048
23. Israeli M, Ben-Gal T, Yaari V, et al. Individualized immune monitoring of cardiac transplant recipients by noninvasive longitudinal cellular immunity tests. Transplantation. Apr 27 2010; 89(8): 968-76. PMID 20075792
24. Kobashigawa JA, Kiyosaki KK, Patel JK, et al. Benefit of immune monitoring in heart transplant patients using ATP production in activated lymphocytes. J Heart Lung Transplant. May 2010; 29(5): 504-8. PMID 20133166
25. Gupta S, Mitchell JD, Markham DW, et al. Utility of the Cylex assay in cardiac transplant recipients. J Heart Lung Transplant. Aug 2008; 27(8): 817-22. PMID 18656792
26. Shearer GM, Clerici M. In vitro analysis of cell-mediated immunity: clinical relevance. Clin Chem. Nov 1994; 40(11 Pt 2): 2162-5. PMID 7955403
27. Cheng JW, Shi YH, Fan J, et al. An immune function assay predicts post-transplant recurrence in patients with hepatocellular carcinoma. J Cancer Res Clin Oncol. Oct 2011; 137(10): 1445-53. PMID 21809031
28. Dong JY, Yin H, Li RD, et al. The relationship between adenosine triphosphate within CD4(+) T lymphocytes and acute rejection after liver transplantation. Clin Transplant. 2011; 25(3): E292-6. PMID 21470308
29. Hashimoto K, Miller C, Hirose K, et al. Measurement of CD4+ T-cell function in predicting allograft rejection and recurrent hepatitis C after liver transplantation. Clin Transplant. 2010; 24(5): 701-8. PMID 20047619
30. Cabrera R, Ararat M, Soldevila-Pico C, et al. Using an immune functional assay to differentiate acute cellular rejection from recurrent hepatitis C in liver transplant patients. Liver Transpl. Feb 2009; 15(2): 216-22. PMID 19177434
31. Narasimhan M, Mahimainathan L, Clark AE, et al. Serological Response in Lung Transplant Recipients after Two Doses of SARS-CoV-2 mRNA Vaccines. Vaccines (Basel). Jun 30 2021; 9(7). PMID 34208884
32. Piloni D, Magni S, Oggionni T, et al. Clinical utility of CD4+ function assessment (ViraCor-IBT ImmuKnow test) in lung recipients. Transpl Immunol. Jul 2016; 37: 35-39. PMID 27095000
33. Husain S, Raza K, Pilewski JM, et al. Experience with immune monitoring in lung transplant recipients: correlation of low immune function with infection. Transplantation. Jun 27 2009; 87(12): 1852-7. PMID 19543064
34. Bhorade SM, Janata K, Vigneswaran WT, et al. Cylex ImmuKnow assay levels are lower in lung transplant recipients with infection. J Heart Lung Transplant. Sep 2008; 27(9): 990-4. PMID 18765191
35. Shino MY, Weigt SS, Saggar R, et al. Usefulness of immune monitoring in lung transplantation using adenosine triphosphate production in activated lymphocytes. J Heart Lung Transplant. Sep 2012; 31(9): 996-1002. PMID 22884386
36. Ravaioli M, Neri F, Lazzarotto T, et al. Immunosuppression Modifications Based on an Immune Response Assay: Results of a Randomized, Controlled Trial. Transplantation. Aug 2015; 99(8): 1625-32. PMID 25757214
37. Manga K, Serban G, Schwartz J, et al. Increased adenosine triphosphate production by peripheral blood CD4+ cells in patients with hematologic malignancies treated with stem cell mobilization agents. Hum Immunol. Jul 2010; 71(7): 652-8. PMID 20381567
38. Gesundheit B, Budowski E, Israeli M, et al. Assessment of CD4 T-lymphocyte reactivity by the Cylex ImmuKnow assay in patients following allogeneic hematopoietic SCT. Bone Marrow Transplant. Mar 2010; 45(3): 527-33. PMID 19718067
39. Ashokkumar C, Talukdar A, Sun Q, et al. Allospecific CD154+ T cells associate with rejection risk after pediatric liver transplantation. Am J Transplant. Jan 2009; 9(1): 179-91. PMID 18976293
40. Ashokkumar C, Soltys K, Mazariegos G, et al. Predicting Cellular Rejection With a Cell-Based Assay: Preclinical Evaluation in Children. Transplantation. Jan 2017; 101(1): 131-140. PMID 26950712
41. Das A, Feller M, Ahn J, et al. Assessing the adequacy of immunosuppression in pediatric liver transplantation with immune Monitoring: Are we there yet?. Hum Immunol. Sep 2025; 86(5): 111580. PMID 40912176
42. Allen UD, Preiksaitis JK. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. Sep 2019; 33(9): e13652. PMID 31230381
43. Preiksaitis J, Allen U, Bollard CM, et al. The IPTA Nashville Consensus Conference on Post-Transplant lymphoproliferative disorders after solid organ transplantation in children: III - Consensus guidelines for Epstein-Barr virus load and other biomarker monitoring. Pediatr Transplant. Feb 2024; 28(1): e14471. PMID 37294621
44. Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. Jun 2018; 102(6): 900-931. PMID 29596116
45. Kotton CN, Kumar D, Caliendo AM, et al. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation. Apr 15 2010; 89(7): 779-95. PMID 20224515
46. Kotton CN, Kumar D, Manuel O, et al. The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation. Transplantation. Jul 01 2025; 109(7): 1066-1110. PMID 40200403

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.
March 2025	Replace policy	Policy updated with literature review through November 25, 2024; no references added. Policy statements unchanged.
March 2026	Replace policy	Policy updated with literature review through October 22, 2025; references added. Policy statements unchanged.