



MASSACHUSETTS

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Medical Policy Immune Cell Function Assay

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Policy Number: 182

BCBSA Reference Number: 2.04.56 (For Plan internal use only)

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

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 stem cell transplantation is considered [INVESTIGATIONAL](#).

Use of immune cell function assay testing for all other indications is considered [INVESTIGATIONAL](#).

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is not a covered service.
Commercial PPO and Indemnity	This is not a covered service.
Medicare HMO Blue SM	This is not a covered service.
Medicare PPO Blue SM	This is not a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
81560	Transplantation medicine, measurement of donor and third party-induced CD154+T-cytotoxic memory cells
86352	Cellular function assay involving stimulation (e.g., mitogen or antigen) and detection of biomarker (e.g., ATP)

Description

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.

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 posttransplant 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 pretransplant samples, the threshold for IR is 1.23.

Summary

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 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.

Policy History

Date	Action
1/2024	Annual policy review. References updated. Policy statements unchanged.
2/2023	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
2/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2022	Clarified coding information.
2/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.

2/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
3/2018	Annual policy review. New references added.
1/2017	Annual policy review. New references added.
2/2016	Annual policy review. New references added.
11/2015	Added coding language.
12/2014	Annual policy review. New references added.
2/2014	Annual policy review. New references added.
11/2011-4/1012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
1/2011	References added.
11/2010	Medical Policy Group- Gastroenterology, Nutrition and Organ Transplantation No changes to policy statements.
5/2010	New medical policy. Effective 5/1/2010.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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 November 17, 2023..
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 November 16, 2023.
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, Lopez-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. Torio A, Fernandez EJ, Montes-Ares O, et al. Lack of association of immune cell function test with rejection in kidney transplantation. *Transplant Proc.* Jul-Aug 2011; 43(6): 2168-70. PMID 21839223
14. Zhou H, Wu Z, Ma L, et al. Assessing immunologic function through CD4 T-lymphocyte adenosine 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 (immuknow) 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.* May-Jun 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.* Sep-Oct 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, Oggioni 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. Borade 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, Saggart 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. 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
42. 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
43. 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