Immune Cell Function Assays in Transplantation

Clinical Policy ID: CCP.1363

Recent review date: 3/2026

Next review date: 7/2027

Policy contains: ImmuKnow; immune cell function assay; immunosuppression; Pleximmune; solid organ transplant.

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Coverage policy

See also CCP.1067 Interferon gamma release assays for tuberculosis screening.

Pleximmune® (Plexision Inc., Pittsburgh, Pennsylvania) is investigational/not clinically proven and, therefore, not medically necessary to predict rejection in transplantation.

ImmuKnow® (Eurofins Viracor LLC, Lenexa, Kansas, formerly Cylex, Inc.) is clinically proven and, therefore, may be medically necessary to determine the immunological status, risk of infection, and need for adjustment of immunosuppression in liver transplant recipients aged 18 years and older (American Association for the Study of Liver Diseases, in conjunction with the American Society of Transplantation [Te, 2025]).

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Standard of care patient evaluation and management by a network transplantation health care provider.

Background

Cellular immune function is an important factor in determining risk for acute graft rejection, opportunistic infection, and cancer among immunosuppressed transplant recipients. Immune status monitoring is necessary to balance the risk of immunosuppressant therapy and drug-related toxicity. The most frequently used tools to monitor immunosuppression in transplant recipients are therapeutic drug levels in the blood, antihuman leukocyte antigen antibody assays, and the presence of opportunistic infections, but they are often insufficient to differentiate rejection from toxicity, necessitating allograft biopsy (Bestard, 2017).

Immune cell function assays are tests of biomarkers that quantify T-cell and B-cell alloreactivity noninvasively, which may also provide important information in the management of autoimmune diseases (Bestard, 2017). These tests may address an unmet need for a safer, more tolerable, and cost-effective approach to immunosuppression.

Pleximmune is a qualitative prognostic test that measures the inflammatory response of T-cytotoxic memory lymphocytes to donor cells and reports the results as a numeric score called the immunoreactivity index (Plexision, 2020). The index is compared with a rejection-risk threshold developed from testing of more than 200 liver or intestine recipients to assign risk. The U.S. Food and Drug Administration (2014) approved Pleximmune under a Humanitarian Device Exemption for prediction of acute cellular rejection within 60 days after transplantation in patients younger than 21 years old with liver or small bowel transplantation. It is intended to be used in the pre-, early-, and late-transplantation periods in conjunction with biopsy, standard clinical assessment, and other laboratory information (U.S. Food and Drug Administration, 2020).

ImmuKnow measures the adenosine triphosphate response of stimulated peripheral blood lymphocytes (CD4+ T-cells) as an index of lymphocyte activity. The measurement of CD4 activation reflects the degree of immune function (Eurofins Viracor, undated). The U.S. Food and Drug Administration (2002) issued 510(k) clearance for detection of cell-mediated immunity in solid organ transplant recipients receiving immunosuppressive therapy.

Findings

Guidelines

The American Association for the Study of Liver Diseases, in conjunction with the American Society of Transplantation, issued a weak recommendation for peripheral blood biomarkers that measure intracellular adenosine triphosphate after CD4 cell activation (ImmuKnow) to determine the immunological status, risk of infection, and need for adjustment of immunosuppression in the adult liver transplant recipient. The guideline cited Level 3 supportive evidence from Rodrigo (2012) and Ravaioli (2015) but acknowledged that these studies were performed prior to the use of direct-acting antiviral agents, and the results may not be as applicable in the current liver transplant population (Te, 2025). A guideline update on post-transplant management in pediatric liver transplant is in progress (American Association for the Study of Liver Diseases, 2026).

The International Society for Heart and Lung Transplantation does not recommend ImmuKnow in adult and pediatric heart transplant recipients for rejection monitoring. The recommendation was based on data derived from a single randomized clinical trial or large non-randomized studies and evidence or general agreement that

the treatment or procedure is not useful or effective and, in some cases, may be harmful (Class III, Level of Evidence B) (Velleca, 2023).

Evidence review

There is insufficient evidence to support the clinical utility of ImmuKnow or Pleximmune immune cell function assays in solid organ transplantation for predicting either acute graft rejection or infection. The best available evidence for ImmuKnow consists of one randomized controlled trial examining its role in guiding adjustment of immunosuppressive and anti-infective agents in liver transplant recipients (Ravaioli, 2015), meta-analyses of nonrandomized studies, and individual nonrandomized studies that provide mixed results in solid organ transplant populations. Current evidence for Pleximmune consists of validation studies, regulatory submission data, and preliminary studies requiring confirmation. Inconsistent findings, lack of standardized methods and testing interpretation, and individual immune response characteristics limit routine clinical use of these assays in solid organ transplant recipients.

The randomized controlled trial compared outcomes of serial immune function testing after surgery using ImmuKnow (n = 102) and controls/standard practice (n = 100) to guide tacrolimus dosing in liver transplant recipients aged 18 to 70 years. In the ImmuKnow group, tacrolimus doses were reduced by 25% when adenosine triphosphate levels were < 130 nanograms per milliliter (ng/mL) and increased by 25% when adenosine triphosphate levels were > 450 ng/mL. The ImmuKnow group had longer one-year survival (95% versus 82%; $P < .01$) and fewer infections > 14 days after transplant (42.0% vs. 54.9%, $P < .05$) (Ravaioli, 2015).

Two meta-analyses of nonrandomized studies examined the diagnostic and prognostic performance of ImmuKnow in liver and kidney transplant recipients. For predicting infection in kidney transplant recipients, ImmuKnow had a sensitivity of 0.51, specificity of 0.75, a positive likelihood ratio of 1.97, a negative likelihood ratio of 0.67, and a diagnostic odds ratio of 3.56. For predicting acute rejection, the results were sensitivity of 0.51, specificity of 0.90, a positive likelihood ratio of 4.45, a negative likelihood ratio of 0.35, and a diagnostic odds ratio of 13.81 (Wang, 2014).

In Rodrigo's meta-analysis, ImmuKnow demonstrated a sensitivity of 0.84 and a specificity of 0.75 for predicting infection in adult liver transplant recipients. Transplant recipients with a positive ImmuKnow result had 14.6 greater odds of having an infection than patients with a negative test result. A positive likelihood ratio of 3.3 suggests that a positive ImmuKnow result increases the post-test probability of infection. In contrast, ImmuKnow's test performance for acute rejection could not be validated due to considerable heterogeneity across studies (Rodrigo, 2012).

Results of large retrospective studies have been published. In 705 pediatric patients undergoing liver transplantation, Epstein-Barr Virus infection was detected in 468 (66.4%). ImmuKnow assay testing documented a significantly lower overall immune response in infected than non-infected patients ($P < .0001$), supporting the authors' conclusion that ImmuKnow may provide guidance in reducing immunosuppressive agents in treating post-transplant lymphoproliferative disorder (Qin, 2020).

Two large retrospective studies provide conflicting results of the utility of immune cell function assays in heart transplant recipients. The first study found no association between either immune cell function assay levels or CD3 lymphocyte counts and adverse outcomes in 78 pediatric participants (Chen, 2023). In the second study, participants with low pre-transplant ImmuKnow levels had a lower risk of early rejection when compared with patients with moderate or high levels. The mean ImmuKnow level in the non-rejection group was 364.9 ng/mL of adenosine triphosphate compared with 499.3 ng/mL of adenosine triphosphate in the rejection group ($P = .020$) (Maidman, 2022).

Limited studies have evaluated the diagnostic accuracy of the Pleximmune test. The sensitivity and specificity of Pleximmune for predicting acute cellular rejection were 0.84 and 0.80, respectively, in training set-validation set

testing of 214 pediatric liver or intestinal transplant recipients (Ashokkumar, 2017; Sindhi, 2016). A retrospective chart review of 31 pediatric liver transplant recipients, who had both Pleximmune and liver biopsy results, found an inverse correlation between tacrolimus level and the Pleximmune immune reactivity index (r = -0.34; *P* = .039). Sensitivity, specificity, positive predictive value, and negative predictive value for acute cellular rejection was 55%, 65%, 33% and 81%, respectively, and the combination of donor-specific antibody and Pleximmune results had a specificity of 92% and negative predictive value of 89%. The authors recommend confirmation in future research (Das, 2025).

In 2024, we deleted several individual studies that were already analyzed in the systematic reviews and meta-analyses included in this policy, and updated the references. No policy changes are warranted.

In 2025, we identified no newly published, relevant literature to add to the policy. No policy changes are warranted.

In 2026, we updated the references and added medical necessity criteria for ImmuKnow based on new guideline recommendations.

References

On January 30, 2026, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “ImmuKnow,” “immune cell function,” and “Pleximmune.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

2/2018: initial review date and clinical policy effective date: 4/2018

12/2019: policy references updated.

3/2021: policy references updated.

3/2022: Policy references updated.

3/2023: Policy references updated.

3/2024: Policy references updated.

3/2025: Policy references updated.

3/2026: Policy references updated. Coverage modified.

Related codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1363. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code description
86352	Cellular function assay involving stimulation (e.g. mitogen or antigen) and detection of biomarker (e.g., ATP)
81560	Transplantation medicine (allograft rejection, pediatric liver and small bowel), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score
0018M	Transplantation medicine (allograft rejection, renal), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score