Immune cell function assays in transplantation

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Policy contains: Immune cell function assay; immunosuppression; graft vs host; organ transplantation.

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Coverage policy

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

Immune cell function assays (e.g., ImmuKnow® [Cylex, Inc. now manufactured by Viracor Eurofins Inc., Lee's Summit, Missouri] or Pleximmune® [Plexision Inc., Pittsburgh, Pennsylvania]) to predict rejection and infection in transplantation are investigational/not clinically proven and, therefore, not medically necessary.

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 allograph biopsy (Bestard, 2017).

Immune cell function assays are 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

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 less 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

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) approval for detection of cell-mediated immunity in solid organ transplant recipients receiving immunosuppressive therapy.

Findings

There is insufficient evidence to support the clinical utility of ImmuKnow or Pleximmune immune cell function assays in solid organ transplantation. The best available evidence for ImmuKnow consists of one randomized control trial to guide adjustment of immunosuppressive and anti-infective agents in solid organ transplant recipients (Ravaioli, 2015) and several retrospective studies that provide mixed results. Current evidence for Pleximmune consists of validation studies and regulatory submission data. 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 American Society of Transplantation does not mention the use of the ImmuKnow immune cell function assay in its recommendations for the screening, monitoring, and reporting of infections and complications in the evaluation of recipients of organ transplantation (Humar, 2006, reaffirmed 2013). An article representing the Society's position notes the large variability in sensitivity (ability to detect early viral infection) in transplant patients); the 11 types of assays listed do not include immune cell function assay (Fishman, 2009).

A meta-analysis of six studies determined that, for predicting infection, 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. The authors concluded that the data did not support the use of the ImmuKnow assay to predict or monitor the risks of infection and acute rejection in renal transplant recipients (Wang, 2014).

A meta-analysis assessed ImmuKnow as a diagnostic tool for predicting infection (five studies) and acute rejection (five studies) in adults after liver transplantation. For predicting infection, ImmuKnow demonstrated a sensitivity of 0.84 and a specificity of 0.75. According to the diagnostic odds ratio, transplant recipients with a

positive ImmuKnow result had 14.6 greater odds of having an infection than patients with a negative test result, and 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).

A meta-analysis of nine studies in post-transplantation recipients determined that the pooled estimates for identifying infection risk were poor, with a sensitivity of 0.58, a specificity of 0.69, a positive likelihood ratio of 2.37, a negative likelihood ratio of 0.39, and a diagnostic odds ratio of 7.41. The pooled estimates for identifying risk of rejection were also fairly poor with a sensitivity of 0.43, a specificity of 0.75, a positive likelihood ratio of 1.30, a negative likelihood ratio of 0.96, and a diagnostic odds ratio of 1.19 (Ling, 2012).

A review of 1,031 ImmuKnow assays among 362 kidney, liver, and pancreas transplant patients found that by January 31, 2010, 14.4% with more than one assay below 175 nanograms/milliliter (ng/mL) were deceased, versus 5.2% with all assays at least 175 ng/mL (P = .0053), suggesting ImmuKnow can predict short-term mortality. No difference existed in rejection between the two groups (19.8% versus 17.5%, P = .66) (Berglund, 2011).

An analysis of 897 T-cell assay (ImmuKnow) results in 414 renal transplant patients showed nearly 40% of patients experienced a decrease of > 150 ng/mL from one to six months after the procedure (P < .0001). The decrease flattened in the period six to 12 months after (P = .33). T-cell assay ≤ 225 ng/mL was associated with human polyomavirus 1 virus infection only at 12 months (P = .005), suggesting that patients with low values after six months may benefit from tailoring of immunosuppression or more monitoring to prevent infection (Gralla, 2012).

An article on 248 recipients of liver transplants showed the average ImmuKnow adenosine triphosphate value in the 109 patients who developed invasive fungal infections was significantly lower than that in those with common bacterial infections (P < .01) or stable liver recipients (P < .01). Thus, ImmuKnow assays may identify patients at risk of developing such infections after liver transplantation (Zhou, 2011).

A study of 4,224 assay values in 306 renal transplantation patients showed that average ImmuKnow assay levels (reported as ng/mL) after transplant were 461 (zero to one week), 519 (one week to one month), 411 (one to three months), 344 (three to 12 months), and 405 (thereafter). This trend was similar to that of peripheral white blood cell counts (P < .0001) but did not correspond with risk of infection/rejection. ImmuKnow assay results should be interpreted cautiously (Sageshima, 2014).

A review of 1,095 blood samples from 656 renal transplant recipients and 200 samples from controls (healthy blood donors) analyzed with the ImmuKnow assay did not support use of the assay as an immune monitoring test after transplantation in clinically stable transplantation patients. Authors support intracellular adenosine triphosphate measurement in CD4 T-cells as the preferred method of estimating T-cell activation capacity (Vittoraki, 2014).

A randomized controlled study of 202 liver transplant recipients compared outcomes of serial immune function testing after surgery using ImmuKnow (n = 102) and controls/standard practice (n = 100) to guide tacrolimus dosing. In the ImmuKnow group, tacrolimus doses were reduced 25% when adenosine triphosphate levels were < 130 ng/mL and increased 25% when adenosine triphosphate 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).

A review of $CD4^+$ T-cell intracellular adenosine triphosphate levels analyzed by ImmuKnow assay in 273 liver transplantation patients concluded survival is correlated with these levels, the peak occurring in the first three months following the procedure (Qu, 2017).

A study of 705 pediatric patients undergoing liver transplantation detected Epstein-Barr Virus infection 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).

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 lung or intestinal transplant recipients (Ashokkumar, 2017; Sindhi, 2016).

In 2024, we deleted several individual studies that were already analyzed in the systematic reviews and meta-analyses included in this policy. We added two large retrospective studies providing 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 of 81 cardiac transplant recipients, 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 the 364.9 ng/mL of adenosine triphosphate compared with 499.3 ng/mL of adenosine triphosphate in the rejection group ($P = .020$) (Maidman, 2022). No policy changes are warranted.

References

On December 22, 2023, 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 assay," 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

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