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Immune Cellular Function Assay to Monitor and Predict Immune Function

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Related Policies (if applicable)
None

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Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Use of an immune cell function assay to monitor and predict immune function after solid organ transplantation **may be considered medically necessary**.

Use of an immune cell function assay **is considered experimental, investigational and/or unproven** for all other indications, including but not limited to monitoring and predicting immune function after hematopoietic stem cell transplantation.

Policy Guidelines

None.

Description

Careful monitoring of lifelong immunosuppression is required to ensure long-term viability of solid organ allografts without incurring 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.

Immunosuppression for Transplant

In current clinical practice, levels of immunosuppression in patients being managed after solid organ transplant or hematopoietic cell transplantation are determined by testing for clinical toxicity (e.g., 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 the patient's peripheral blood lymphocytes. CD154 is a marker of inflammatory response. To characterize 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 post-transplant 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.

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 cell-mediated immune response in populations undergoing immunosuppressive therapy for 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 cell-mediated immune response in an immunosuppressed population. In 2010, a device modification for this assay was cleared for marketing by the FDA through the 510(k) process (K101911). There were no changes to the indications or intended use. (1)

In August 2014, Pleximmune™ (Plexision, Pittsburgh, PA) 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 post-transplantation 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

This policy was originally created in 2010 and has been updated periodically with review of the literature using the PubMed database, most recently for the period through September 2022.

Medical policies assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Medical policies assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of this policy, and credible information on technical reliability is available from other sources.

IMMUNE CELL FUNCTION TESTING

The immune cell function assays are generally not meant to diagnose a condition (infection or rejection) that is concurrently present or absent, instead, the assays are designed to predict future risk of infection or rejection. Thus, although many studies have evaluated immune function assays using these measures, they are not the ideal method to assess the value of the test, because these measures will be sensitive to the specific context of the study and will vary according to study characteristics (e.g., time horizon, baseline risk of outcome). Risk stratification can result in improved health outcomes if specific clinical interventions are based on the test results and also decrease the risk of a poor health outcome.

In the case of immune cell function tests, it is proposed that immunosuppression regimen can be modified based on test results to minimize the risk of infection or rejection. Ideally, clinical trials comparing management of transplant patients with or without immune function testing would provide robust evidence of clinical utility. Lacking such trials, clinical utility might be inferred by a strong chain of logic that would link evidence on the predictive characteristics of the immune function assay and evidence that the interventions based on test results would produce the desired outcomes.

Clinical Context and Test Purpose

The purpose of immune cell function assay testing in patients who have received solid organ or hematopoietic cell transplant (HCT) is to inform treatment and management decisions with immunosuppressive therapy.

The question addressed in this medical policy is: Does immune cell function assay testing improve the net health outcome in individuals who have received solid organ or HCTs?

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are individuals who have a solid organ transplant or an HCT.

Interventions

The test being considered is immune cell function testing with ImmuKnow or Pleximmune.

Comparators

The following practices are currently being used to manage solid organ and HCTs: standard monitoring of immunosuppression for those who have solid organ transplants and standard of care for those with HCTs.

Outcomes

The general outcomes of interest are acute and chronic rejection episodes, graft dysfunction, graft survival, morbidity associated with graft dysfunction and overall survival (OS) post-transplant.

Acute rejection following any transplant typically occurs within weeks, with the highest risk during the first 3 months, and rarely occurs years after transplant. Chronic rejection typically develops years after transplant.

Study Selection Criteria

For the evaluation of clinical validity of immune cell function testing, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores);
- Included a suitable reference standard;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

ImmuKnow Test for Solid Organ Transplants

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Numerous studies have evaluated ImmuKnow testing in relation to risk of future infection or rejection. In general, these studies have assessed the test using measures for assessing diagnostic tests. The studies tend to show that test results correlate with either infection or rejection at specified thresholds, but that diagnostic characteristics tend to show poor sensitivity and poor specificity. This is to be expected of a test that is not meant as a diagnostic tool but as a risk-stratification tool. Systematic reviews of ImmuKnow are first summarized, followed by individual studies of solid organ transplantation, organized by transplant type.

Systematic Reviews

Ling et al. (2012) performed a meta-analysis of studies (published to July 2011) to assess the efficacy of ImmuKnow for identifying risks of infection and rejection in adult transplant recipients. (3) Nine studies published between 2008 and 2011 met inclusion criteria. Meta-analysis of these 9 studies incorporated 2458 samples from transplant recipients, including 172 samples from patients with infection and 135 samples from patients with rejection. Three studies were of liver transplant recipients, three of kidney recipients, and one each of heart, lung, and mixed organ transplant recipients. Pooled estimates of ImmuKnow performance characteristics for identifying infection risk were: sensitivity of 58% (95% confidence interval [CI], 52% to 64%), specificity of 69% (95% CI, 66% to 70%), positive likelihood ratio of 2.37 (95% CI, 1.90 to 2.94), negative likelihood ratio of 0.39 (95% CI, 0.16 to 0.70), and diagnostic odds ratio of 7.41 (95% CI, 3.36 to 16.34). Pooled estimates for ImmuKnow for identifying risk of rejection were: sensitivity of 43% (95% CI, 34% to 52%), specificity of 75% (95% CI, 72% to 78%), positive likelihood ratio of 1.30 (95% CI, 0.74 to 2.28), negative likelihood ratio of 0.96 (95% CI, 0.85 to 1.07), and diagnostic odds ratio of 1.19 (95% CI 0.65 to 2.20). Due to significant heterogeneity across studies, reviewers conducted subgroup analyses in liver and renal transplant recipients. The liver transplantation group had a pooled sensitivity of 85%, and the

renal transplantation group had a specificity of 80%, indicating that different types of organ transplanted may be a source of observed heterogeneity.

Rodrigo et al. (2012) conducted a systematic review and meta-analysis to identify studies (published to March 2012) documenting the use of ImmuKnow to monitor immune function in adult liver transplant recipients. (4) Five studies analyzed ImmuKnow performance in infection (651 patients) and 5 in acute rejection (543 patients). Two (of 5) studies also were included in the previously discussed systematic review by Ling et al. (2012). Pooled sensitivity, specificity, positive likelihood ratio, diagnostic odds ratio (DOR), and mean standard deviation (SD) area under the summary receiver operating characteristic (ROC) curve for infection were 84% (95% CI, 78% to 88%), 75% (95% CI, 71% to 79%), 3.3 (95% CI, 2.8 to 4.0), 14.6 (95% CI, 9.6 to 22.3), and 0.824 (0.034), respectively. Pooled estimates for acute rejection were 66% (95% CI, 55% to 75%), 80% (95% CI, 76% to 84%), 3.4 (95% CI, 2.4 to 4.7), 8.8 (95% CI, 3.1 to 24.8), and 0.835 (0.060), respectively. Heterogeneity was low for infection and high for acute rejection studies. These findings suggested that ImmuKnow could be considered a valid tool to assess infection risk in adult liver transplant recipients.

Pediatric Transplants

Rossano et al. (2009) studied 83 pediatric patients (median age, 4.9 years) undergoing heart transplant. (5) ImmuKnow was performed at routine follow-up visits from 3 months to more than 5 years after transplant. There were 26 episodes of acute rejection, 20 (77%) of which were cell-mediated, and the remainder were humoral rejection. There were 38 infections. No difference in adenosine triphosphate (ATP) production as measured by ImmuKnow was detected between patients with or without acute rejection or with or without infection. Further, the manufacturer's reported risk ranges for rejection (ATP production ≥525 ng/mL) or infection (ATP production ≤225 ng/mL) were not predictive of rejection or infection, respectively. The studies noted, however, it may be that pediatric patients' risks for post-transplant infection and rejection correspond to different ATP production levels.

Liu et al. (2019) found a correlation between low ATP levels and infection following a living-donor liver transplantation in pediatric patients. (6) The retrospective analysis evaluated 66 patients from a single center in China. The patients were divided into 2 groups: those who were diagnosed with an infection post-transplant (n=28) and those who did not develop an infection (n=38). ImmuKnow testing was performed pre-transplant and at 1 to 4 weeks, 2 months, and 3 months post-transplant. The mean pre-transplant ATP level in the overall cohort was 302.5±195.7 ng/ml. The post-transplant ATP levels were significantly lower in the infection group (188.6±93.5) compared to the non-infection group (424.4±198.1 ng/ml; $p<.05$). An ROC curve was generated to determine a reference ATP level for the diagnosis of infection. At an ATP level of 200.5 ng/mL in patients diagnosed with an infection, the sensitivity and specificity were 89.5% and 64.3%, respectively; the area under the curve (AUC) was 0.866.

Kidney Transplants

A retrospective study of kidney transplant recipients found statistically significant correlations between ATP production and white blood cells (WBCs). The study of 39 patients at a single

center in Japan, Nishikawa et al. (2014) reported correlation coefficients (R^2) of 0.573 (p=0.03) and 0.510 (p=0.02) for associations between WBC and neutrophil counts, respectively. (7) In this study, ATP levels in 5 patients who developed viral infections in the early post-transplantation period (<50 days) were within normal limits. However, those in the late period were significantly lower than 200ng/ml (421.0 ± 062.6 for early vs 153.7 ± 72.7 for late; P = .02). Multiple regression analyses indicated that peripheral white blood cell and neutrophil counts affected Immuknow (IMK) values (P =.03 and P =.02, respectively). The authors concluded the IMK assay to be a useful test for identifying patients at risk for post-transplantation viral infection in the late transplant period.

Torio et al. (2011) grouped 227 samples from 116 kidney transplant recipients (mean age, 51.2 years; range, 19-77 years) by clinical course: stable (no infectious syndrome or acute rejection episode 1 month before and after immune cell assay; n=168), infection (fever plus at least 1 positive culture or positive polymerase chain reaction [PCR]; n=24), or rejection (biopsy-proven acute rejection; n=35). (8) Healthy blood donors served as controls (n=108). Immunosuppressive regimens included pretransplant basiliximab (an interleukin-2 receptor inhibitor) or antithymocyte globulin and post-transplant tacrolimus, mycophenolate mofetil, and corticosteroid, or calcineurin inhibitors. Mean (SD) ATP production in the stable group (375.3 [140.1] ng/mL) and in the control group (436.5 [112.0] ng/mL) were higher than in the infection group (180.5 [55.2] ng/mL; p<0.001 for both comparisons).

Zhou et al. (2011) grouped 259 Chinese kidney transplant recipients (mean age, 38.8 years) by clinical course: stable (no adverse events 7 days before and after immune cell assay; n=174), infection (clinical and imaging evidence of infection within 7 days before or after assay; n=32), rejection (biopsy-proven acute rejection diagnosed within 7 days before or after assay without antirejection therapy; n=16), or methylprednisolone (intravenous methylprednisolone given to treat biopsy-proven acute rejection within 3 days before or after assay; n=33). (9) Post-transplant immunosuppressive regimens included corticosteroids, calcineurin inhibitors, and mycophenolate mofetil. Median ATP production in the infection group (116.4 ng/mL; range, 66.3-169.2 ng/mL) and the methylprednisolone group (182.3 ng/mL; range, 113.6-388.8 ng/mL) was lower than in the stable group (347.7 ng/mL; range, 297.9-411.7 ng/mL; p<0.001 for both comparisons). Median ATP production in the rejection group was higher than in the stable group (615.9 ng/mL; range, 548.8-743.5 ng/mL; p<0.001). ROC curve analysis was evaluated to determine optimal ATP cutoffs for infection and rejection in this sample. With a cutoff for infection of 238 ng/mL, the sensitivity and specificity were 93% and 100%, respectively (AUC=0.991). For rejection, a cutoff of 497 ng/mL maximized the sensitivity and specificity at 92% and 94%, respectively (AUC=0.988).

Reinsmoen et al. (2008) studied 126 kidney transplant recipients to determine whether pretransplant immune parameters (ATP production, human leukocyte antigen [HLA] mismatch, HLA-specific antibodies, and interferon-gamma precursor frequencies to donor or third-party cells) were associated with post-transplant early acute rejection, unstable creatinine course, and poor graft outcome. (10) Mean (SD) pretransplant ATP production in recipients who had no clinical reason for a biopsy was significantly lower (285.3 [143.2] ng/mL) than those in

recipients who had biopsy-proven acute rejection at any post-transplant time point up to 36 months (414.3 [138.5] ng/mL). Recipients who underwent biopsy but had no diagnosis of acute cellular or antibody-mediated rejection had an intermediate value of 333.7 (156.3) ng/mL. Mean (SD) pretransplant ATP production were also significantly higher for recipients with early (<90 days) unstable creatinine levels (362.8 [141.2] ng/mL), a significant predictor of early acute rejection, than for recipients with stable creatinine values (283.4 [146.4] ng/mL). Post hoc analysis using a cutoff ATP production of 375 ng/mL revealed that recipients with pretransplant ATP greater than 375 ng/mL were significantly more likely to experience acute rejection (OR=3.67; 95% CI, 1.195 to 11.201).

In a 2014 prospective study of 67 patients undergoing kidney transplant, patients with low preoperative ATP production had statistically fewer rejection episodes than those with high preoperative ATP production ($p<0.001$). (11) The cutoff used for this analysis was 300 ng/mL. To optimize ImmuKnow performance, Quaglia et al. (2014) (12) and Wang et al. (2014) (13) both proposed assessing change in ATP production over time, rather than single values. In a retrospective study of 118 patients, Quaglia et al. reported an AUC of 0.632 (95% CI, 0.483 to 0.781) for infection risk using a cutoff of -30 ng/mL for the decrease in ATP production from month 1 to month 3. (12) In a prospective study of 140 patients, Wang et al. reported an AUC of 0.929 for risk of acute rejection using a cutoff of 172.55 ng/mL for the increase in ATP production from "right before" the rejection episode to the occurrence of rejection. (13)

Heart Transplants

Several studies have examined ATP production in adult heart transplant recipients. Weston et al. (2020) evaluated use of ImmuKnow in heart transplant recipients with severe systemic infections. (14) Patients were followed at the time of scheduled biopsy and weekly with the ImmuKnow assay if diagnosed with a systemic infection. On detection of a systemic infection, maintenance immunosuppression, typically mycophenolate mofetil or azathioprine, was withdrawn and tacrolimus dose was reduced by 50%. Weekly ImmuKnow levels informed further dose reductions of tacrolimus, but the procedure for these reductions was not reported. Maintenance immunosuppression was restarted once the infection was cleared and ImmuKnow levels increased to greater than 225 ng/mL. Thirteen patients had severe systemic infections accounting for 16 total infectious episodes. At the time of the infection, the mean ImmuKnow level was 109 ± 49 ng/mL (from 311 ± 118 ng/mL prior to the diagnosis) and increased to 315 ± 135 ng/mL after the infection cleared ($p<0.01$). The ImmuKnow level during the infection also correlated with the underlying infectious microorganism. Infections caused by a virus, fungus, or bacteria had mean ImmuKnow levels of 75 ng/mL, 95.07 ng/mL, and 123.4 ng/mL, respectively. Patients without infections or non-severe systemic infections served as a control group (n=67). The control group had a mean ImmuKnow level of 294 ± 167 ng/mL. There were 8 episodes of moderate rejection and 6 episodes of severe rejection out of a total of 435 endomyocardial biopsies and 7 episodes of infection in the control group. The mean ImmuKnow level in patients with rejection was 368.7 ng/mL and with infection was 183.3 ng/mL. The authors concluded heart transplant recipients with severe systemic infections presented with a decreased ImmuKnow®, suggesting over immunosuppression. ImmuKnow®

can be used as an objective measurement in withdrawing immunosuppression in heart transplant recipients with severe systemic infections.

Israeli et al. (2010) correlated ImmuKnow results with clinical status in 50 immunosuppressed heart transplant recipients (median age, 58.5 years). (15) Median ATP production for 280 blood samples collected from patients during clinical quiescence (i.e., good clinical status with normal heart function) was 351 ng/mL. ATP levels were within the manufacturer's "moderate" range of immune function (225-525 ng/mL) in 176 (63%) of these samples. Median ATP production for 22 blood samples collected during episodes of biopsy-proven acute rejection was 619 ng/mL, a statistically significant difference ($p<0.05$). Median ATP production for 19 blood samples collected during episodes of fungal or bacterial infection (i.e., requiring hospitalization for intravenous antimicrobial therapy) was 129 ng/mL, a statistically significant difference from the production during clinical quiescence ($p<0.05$). Results noted that "Longitudinal monitoring of Immuknow levels through serial testing proved to be a reliable method for individual patient immune management." The authors concluded "Immunknow assay reliably reflects the cellular immune function of heart transplantation patients, thereby supporting the immune monitoring and management of these patients. Serial longitudinal Immuknow monitoring allows immune management of therapy according to the individual patient's immune status."

A retrospective study by Kobashigawa et al. (2010) correlated ImmuKnow results from 296 adult heart transplant recipients (mean age, 54.6 years) with infection or rejection episodes occurring within 1 month of assay. (16) Assays were performed between 2 weeks and 10 years post-transplant (N=864). Infection was diagnosed by the treating physician and resulted in antibiotic therapy. Rejection was defined as any treated episode of cellular or antibody-mediated rejection, with or without hemodynamic compromise. Transplant recipients without infection or rejection served as controls (n=818 assays). All patients received immunosuppression with tacrolimus, mycophenolate mofetil, and corticosteroids, without induction therapy. Oral prednisone bolus and taper was used for asymptomatic rejection, and antithymocyte globulin was used for rejection with hemodynamic compromise. Mean (SD) ATP production was lower in patients with infection (187 [126] ng/mL) than in controls (280 [126] ng/mL, $p<0.001$). Ten percent of ATP production less than 200 ng/mL were associated with infection, and 2% of ATP production greater than 200 ng/mL were associated with infection ($p<0.001$). This study suggested that ImmuKnow might be associated with the prediction of infection in heart transplant patients.

Liver Transplants

Cheng et al. (2011) evaluated the capability of ImmuKnow to predict recurrence of hepatocellular carcinoma (HCC) in Chinese patients undergoing liver transplantation for HCC. (17) A threshold ATP production of 175 ng/mL was initially determined from 176 assays of 60 patients with HCC (mean age, 49.8 years), 60 (34%) from patients with recurrent HCC post-transplant and 116 (66%) from stable patients without HCC recurrence, infection, or biopsy-proven rejection. Mean (SD) ATP production in patients with recurrent HCC (137.8 [6.4] ng/mL) were lower than those without recurrence (289.2 [133.9] ng/mL; $p<0.01$). The sensitivity and specificity for the 175-ng/mL threshold value were 83% and 84%, respectively (AUC=0.869).

ImmuKnow was then administered to a second cohort of 92 patients with HCC undergoing liver transplantation (mean age, 50.1 years). Patients were stratified by high immune response (mean ATP production, >175 ng/mL) and low immune response (mean ATP production, ≤175 ng/mL). Seventeen (23%) of 73 patients in the high-response group and 16 (84%) of 19 patients in the low-response group developed HCC recurrence (p<0.001). Mean (SD) ATP production were 295.3 (85.4) ng/mL and 126.6 (37.9) ng/mL in the high- and low-immune response groups, respectively (p<0.001). High immune response was associated with recurrence-free survival (odds ratio [OR], 7.28; 95% CI, 3.23 to 16.13) but not overall survival (OR=2.20; 95% CI, 0.56 to 8.65). This study also correlated ImmuKnow results with clinical status (infection or rejection) among a cohort of the original 60 patients with HCC plus 45 additional patients with nonmalignant liver diseases. ImmuKnow assays were collected during infection (diagnosed by clinical features, positive microbiologic tests, and imaging), biopsy-proven acute or chronic rejection, and stability (defined as good liver function and good general health at least 2 weeks after transplantation, without evidence of infection, rejection, or tumor recurrence). Immunosuppressive regimens were not defined. Rejection episodes were treated with bolus steroids or antithymocyte globulin. Mean (SD) ATP production during infection (145.2 [87.0] ng/mL) and rejection (418.9 [169.5] ng/mL) differed from mean (SD) production during stability (286.6 [143.9] ng/mL, p<0.01 for both comparisons). ROC analysis showed that optimum cutoff for infection was 200 ng/mL, with a sensitivity of 79% and specificity of 75% (AUC=0.842). Optimum cutoff for rejection was 304 ng/mL, with a sensitivity of 80% and specificity of 76% (AUC=0.806). Another retrospective study (2011) of 87 liver transplant recipients used a cutoff for rejection of 407 ng/mL based on ROC curve analysis, with a sensitivity and specificity of 86% and 81%, respectively (AUC=0.869). (18)

To assess ImmuKnow's ability to differentiate ACR from recurrent hepatitis C virus (HCV) infection in patients with liver transplanted due to HCV-related liver disease, Hashimoto et al. (2010) retrospectively reviewed 54 allograft liver transplant recipients who had concomitant ImmuKnow results available (mean age, 52 years; range, 40-63 years). (19) Liver biopsies were performed every 6 months after liver transplantation and when clinically indicated due to elevated liver function tests. Biopsies were read by a pathologist blinded to ImmuKnow results. PCR detection of HCV RNA was not used. Immunosuppressive regimens included basiliximab, calcineurin inhibitors, and mycophenolate mofetil. ImmuKnow assays were collected before biopsy. Results were divided into 4 groups based on biopsy findings: ACR (n=11), recurrent HCV (n=26), normal biopsy (n=12), and overlapping features of both ACR and recurrent HCV. Mean (SD) ATP production in ACR (365 [130] ng/mL; range, 210-666) was higher than in normal biopsy (240 [71] ng/mL; range, 142-387; p=0.006). Mean (SD) ATP production in recurrent HCV (152 [100] ng/mL; range, 20-487) was lower than in both ACR (p<0.001) and normal biopsy (p=0.019). Mean (SD) ATP production of patients with overlapping features of both ACR and recurrent HCV (157 [130] ng/mL; range, 25-355) did not differ statistically from the other groups. Further, 73% of patients with ACR had ATP production within the manufacturer-defined moderate range. Eighty-eight percent of patients with recurrent HCV had ATP production in the low range (p<0.001). ROC curve analysis yielded a cutoff level of 220 ng/mL with sensitivity of 89% and specificity of 91% (AUC=0.93; 95% CI, 0.85 to 1.00).

Cabrera et al. (2009) assessed the ability of ImmuKnow to differentiate between acute cellular rejection (ACR) and recurrent HCV infection in 42 adults with liver transplant due to HCV-related end-stage liver disease. (20) All patients had liver enzyme abnormalities post-transplant and underwent liver biopsy to diagnose both ACR and recurrent HCV. The most sensitive indicator of HCV infection (HCV RNA detection by PCR) was not used to diagnose HCV. ImmuKnow was performed with blood collected before biopsy, and biopsy samples were interpreted by histopathologists blinded to ImmuKnow results. Median ATP production in 12 patients diagnosed with ACR was 283.3 ng/mL (range, 241.1-423.0 ng/mL), and median ATP production in 15 patients diagnosed with recurrent HCV was 148.0 ng/mL (range, 33.7-186.0 ng/mL), a statistically significant difference ($p<0.001$). Median ATP production in 15 patients with mixed biopsy features of both ACR and recurrent HCV, but predominance of neither, was 234.0 ng/mL (range, 155.3-325.0 ng/mL), a statistically significant difference for both the ACR group ($p=0.02$) and the recurrent HCV group ($p<0.001$). Of note, 100% of patients with recurrent HCV had ATP production within the manufacturer's range for increased risk of infection (<225 ng/mL).

Lung Transplants

Piloni et al. (2016) reported on a retrospective cohort study evaluating the immunosuppressive association between oversuppression (ImmuKnow score, corresponding to intracellular ATP, ≤226 ng/mL) and adequate or undersuppression (ImmuKnow score, >226 ng/mL) in a sample of 61 patients in follow-up for lung transplantation. (21) ImmuKnow testing had been performed at 6-month follow-up for patients who entered the study at the time of transplant (n=28); for other patients, testing was obtained on an as-needed basis because of acute graft dysfunction or suspected immune oversuppression. Being in the immune oversuppression group was associated with higher odds of infection (51 cases of infection/71 ImmuKnow tests vs 25/56; OR=2.754; 95% CI, 1.40 to 5.39; $p=0.003$).

Husain et al. (2009) assessed the correlation between ImmuKnow results and different types of infections (bacterial, fungal, viral) in 175 adult lung transplant recipients receiving immunosuppression induction with alemtuzumab. (22) Blood samples were collected prospectively as part of routine surveillance in all patients during 2 to 48 months of follow-up. Periods of stability were defined as no infection occurring 1 month before or after the blood draw. For infectious episodes, only ATP levels drawn within 1 month before the episode were analyzed. Median ATP production during stability was 175 ng/mL (25th-75th percentile, 97-306 ng/mL). Significantly lower median ATP production was seen in 13 CMV infections (49 ng/mL, $p<0.001$) and 14 bacterial pneumonias (92 ng/mL, $p=0.002$). Median ATP production for fungal disease (85 ng/mL) did not differ significantly from that in stability (p not reported). Four patients who developed invasive pulmonary aspergillosis all had ATP levels less than 50 ng/mL. Generalized estimating logistic regression analysis demonstrated an odds ratio of 2.81 (95% CI, 1.48 to 4.98) for increased risk of infection with ATP levels less than 100 ng/mL and an odds ratio of 9 (95% CI not reported) with values less than 50 ng/mL.

Bhorade et al. (2008) assessed the relation between low post-transplant ATP production (≤225 ng/mL) and recent infection in 57 immunosuppressed adult lung transplant recipients. (23)

ImmuKnow assays were performed in 143 patients at routine clinic visits when each patient was on a stable dose of tacrolimus. Fifteen patients developed infections (bacterial or fungal pneumonia, CMV infection); 14 (93%) of the 15 had ATP production less than 225 ng/mL at the time of their infections (sensitivity, 93%). Among the 42 noninfected patients, 16 (38%) had ATP production less than 225 ng/mL (specificity, 62%).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

The only study comparing patients managed with and without immune response assays is a study by Ravaioli et al. (2015). (24) This randomized trial included 202 liver transplant patients. One group was randomized to have ImmuKnow testing at periodic intervals after transplant, and at clinically indicated times after a suspected or confirmed rejection or infection event. In this group, tacrolimus doses were reduced 25% when ImmuKnow values were less than 130 ng/mL and increased by 25% when ImmuKnow values were greater than 450 ng/mL. In the control group, ImmuKnow testing was performed but not revealed to treating physicians, and tacrolimus was managed according to standard practice. Declared study outcomes were survival, infection rate, rejection rate, and graft loss. One-year survival was 95% in the ImmuKnow group and 82% in the control group ($p<0.01$).

Section Summary: ImmuKnow Test for Solid Organ Transplants

For solid organ transplants, 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. The trial of ImmuKnow test in liver transplant patients showed improvement in overall survival.

ImmuKnow Test for Hematopoietic Cell Transplants

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Two studies examined the association between ImmuKnow and prognosis in hematopoietic cell transplantation (HCT), one in autologous transplants and one in allogeneic transplants. Manga et al. (2010) assessed ATP production in 16 adults (mean age, 52 years) with hematologic malignancies (multiple myeloma, B- or T-cell lymphoma, acute myeloid leukemia) undergoing

mobilization with granulocyte-colony stimulating factor (G-CSF) with or without granulocyte-macrophage-colony stimulating factor for autologous HCT. (25) Mean (SD) ATP production on day 5 of G-CSF therapy in 10 patients who survived more than 2 years after mobilization (673 [274] ng/mL) was higher compared with 5 patients who died within 2 years (282 [194] ng/mL; p=0.014). ROC curve analysis identified a cutoff of 522 ng/mL for predicting patient survival, with a sensitivity and specificity of 80% and 100%, respectively (AUC=0.880). Gesundheit et al. (2010) examined 170 ATP production collected from 40 patients (median age, 34 years; range, 3-64 years) after engraftment of allogeneic HCT for various malignant (acute and chronic myeloid leukemia, acute and chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome, ovarian, breast, and testicular cancer) and nonmalignant (severe aplastic anemia, thalassemia major, adrenoleukodystrophy) diseases. (26) ImmuKnow results were categorized "low" or "normal" according to the manufacturer's ATP cutoff values and correlated with postengraftment clinical course. Overall survival for the immunocompetent ("normal") group was 83% (10/12 patients) at 13 months of follow-up. Overall survival for the immunocompromised ("low") group was 12% (3/25 patients) at 12 months of follow-up. Although test results were associated with outcome, it is unclear how such information could be used to improve patient outcomes.

Subsection Summary: Clinically Valid

Two studies evaluated the association between ImmuKnow and prognosis in HCT. In autologous and allogeneic transplant populations, higher ImmuKnow levels were associated with patients with longer overall survival at 2 years and 12 months, respectively. However, it cannot be determined from these studies whether the discrimination of risk is clinically important and whether there is a compelling chain of evidence that treatment modifications based on predicted risk would improve patient outcomes.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No studies assessing the clinical utility of the ImmuKnow test were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of ImmuKnow testing has not been established for HCTs, a chain of evidence supporting the test's clinical utility cannot be constructed.

Section Summary: ImmuKnow Test for HCTs

For HCTs, the ImmuKnow test has shown associations with longer overall survival for both autologous and allogeneic transplant populations. However, no clinical utility studies were identified. Therefore, it cannot be determined whether the discrimination of risk is clinically important and could potentially alter treatment that would improve patient outcomes

Pleximmune Test for Solid Organ Transplants

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The U.S. Food and Drug Administration (FDA) documents have described a clinical validation study of Pleximmune. (2) Among a sample of 33 pretransplant patients, Pleximmune had 57% sensitivity and 89% specificity for identifying rejection. Among a sample of 64 post-transplant patients, Pleximmune had 84% sensitivity and 80% specificity for identifying rejection. A study by Ashokkumar et al. (2009) evaluated the association between CD154 expression and rejection among pediatric liver transplant patients. (27)

A study by Ashokkumar et al (2017) reported on the preclinical development and validation of an allogeneic-specific CD154-positive T-cytotoxic memory cell test to predict ACR after liver or intestine transplantation inpatients with pediatric liver or lung transplantation. (28) Plexision (manufacturer of Pleximmune) was involved in the study design and assay standardization. A total of 127 patients (120 analyzable samples) were included intel training set (enrolled from 2006 to 2010), and 87 patients (72 analyzable samples) were included in the validation set (enrolled from 2009 to 2012). The training and test sets differed significantly in terms of organ type composition, with a higher proportion of those in the training set represented by liver or liver/small bowel transplant (e.g., 83% liver in training set vs. 71% in validation set; p=.007 for the difference between groups). The IR was defined as the ratio of the reaction of donor-induced CD154-positive T-cytotoxic memory cell to the reaction exceed those induced by reference peripheral blood leukocytes; a ratio above 1 was considered to indicate an increased risk of rejection. An IR of 1.1 or greater as a cutoff in posttransplant samples was associated with an area under the summary ROC curve of 0.878 in the test set (0.791 in the validation set), while a pretransplant IR of 1.23 or greater was associated with a ROC curve of 0.82 in the training set (0.842in the validation set). CD154+T-cytotoxic memory cells predict acute cellular rejection after LTx or ITx in children. Adjunctive use can enhance clinical outcomes.

Pleximmune Test for Hematopoietic Cell Transplants

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

No evidence for the clinical validity of the Pleximmune test for HCT populations was identified.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No evidence for the clinical utility of the Pleximmune test for HCT populations was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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 the clinical validity is uncertain. Therefore, the clinical utility of Pleximmune is unknown for HCTs.

Section Summary: Pleximmune Test for Hematopoietic Cell Transplants

No evidence for the clinical validity or clinical utility of the Pleximmune test for HCT populations were identified.

Summary of Evidence

For individuals who have a solid organ transplant who receive testing using an immune cell function assay with ImmuKnow, the evidence includes numerous studies on the association of assay test values and subsequent rejection or infection, and a randomized controlled trial (RCTs) 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 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. The trial of ImmuKnow test in liver transplant patients showed improvement in overall survival. The use of the assay is considered medically necessary when used according to the U.S. Food and Drug Administration's indications for use and when the criteria outlined in Coverage is met.

For individuals who have a solid organ transplant who receive testing using an immune cell function assay with Pleximmune, the evidence includes the clinical information noted by the Food and Drug Administration (FDA) approval through the humanitarian device exemption process and a report on the test's development and validation. The use of the assay is considered medically necessary when used according to the U.S. FDA indications for use and when the criteria outlined in Coverage is met.

For individuals who have hematopoietic cell transplant (HCT) who receive testing using an immune cell function assay with ImmuKnow, several studies evaluated the association between ImmuKnow and prognosis in HCT. In autologous and allogeneic transplant populations, higher ImmuKnow levels were associated with patients with longer overall survival at 2 years and 12 months. However, it cannot be determined from these studies whether the discrimination of risk is clinically important and whether there is a compelling chain of evidence that treatment modifications based on predicted risk would improve patient outcomes. For individuals who have HCT who receive testing using Pleximmune, no evidence for the clinical utility of the Pleximmune test for HCT populations was identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

Transplantation Society

In 2018, the International Cytomegalovirus Consensus Group of the Transplantation Society (29) updated its consensus statement on the management of cytomegalovirus in solid organ transplant. (30) Routine immunologic monitoring was not recommended.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	81560, 86352
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
07/15/2024	Reviewed. No changes.
12/01/2023	Document updated with literature review. Coverage unchanged. Added reference 29; others updated/removed.
07/15/2022	Reviewed. No changes.
05/01/2021	Document updated with literature review. Coverage unchanged. Added references 6 and 14.
09/15/2020	Reviewed. No changes.
04/15/2019	Document updated with literature review. Coverage unchanged. Added references 27-28.
04/15/2018	Reviewed. No changes.
07/01/2017	Document updated with literature review. Coverage unchanged.
04/15/2016	Reviewed. No changes.
01/15/2015	Document updated with literature review. Coverage unchanged, an example of hematopoietic stem cell transplantation was added to the experimental, investigational and/or unproven statement. The Rationale section has been substantially revised.
01/01/2012	Update of document with literature review. The following was added: Use of an immune cell function assay to monitor and predict immune function after solid organ transplantation may be considered medically necessary. Use of an immune cell function assay for all other indications is considered experimental, investigational and unproven. Document title changed to: Immune Cellular Function Assay to Monitor and Predict Immune Function. CPT/HCPCS code(s) updated.
01/01/2010	New medical policy with literature review. Coverage position is experimental, investigational and unproven.