Policy Replaced with LCD L33418 Effective February 26, 2018

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Immune Cell Function Assay

Policy #: 381
Category: Medicine

Latest Review Date: December 2017
Policy Grade: C

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Careful monitoring of lifelong immunosuppression is required to ensure 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 the immunosuppressive therapy.

Immunosuppression for Transplant

In current clinical practice, levels of immunosuppression in patients being managed after solid organ transplant or hematopoietic cell transplantation (HCT) is determined by evaluating testing for clinical toxicity (e.g., leukopenia, renal failure) and by therapeutic drug monitoring (TDM) 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, gender, and race; circulating drug levels may not reflect the drug concentration in relevant tissues; and levels of an individual immunosuppressant drug may not reflect the cumulative effect of other concomitant immunosuppressants. The main value of TDM is the avoidance of toxic levels. Individual immune profiles, such as an immune cell function assay, could support clinical decision making and help to manage the risk of infection from excess immunosuppression and the risk of rejection from inadequate immunosuppression in immunosuppressed patients.

Treatment

Several commercially available tests of immune cell function have been developed to support clinical decision making.

ImmuKnow® (Cylex) is an immune cell function assay cleared for marketing by the FDA in April, 2002 to detect cell-mediated immunity (CMI) in an immunosuppressed patient population. The assay measures the concentration of adenosine triphosphate (ATP) in whole blood following 15-18 hour incubation with the mitogenic stimulant, phytohemagglutinin (PHA). In cells that respond to stimulation, increased ATP synthesis occurs during incubation. Concurrently, whole blood is incubated in the absence of stimulant for the purpose of assessing basal ATP activity. CD4+ T-lymphocytes are immunoselected from both samples using anti-CD4 monoclonal antibody-coated magnetic particles. After washing the selected CD4+ 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 to fixed ATP level 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 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 increased risk of rejection, and an IR less than 1.1 indicates decreased risk of rejection. For pretransplant samples, the threshold for IR is 1.23.

Policy:

Effective for dates of service on or after May 11, 2012 and prior to February 26, 2018:
Blue Advantage will treat **use of the immune cell function assay to monitor and predict immune function after hematopoietic stem cell transplantation** as a **non-covered** benefit and as **investigational.**

Blue Advantage will treat **use of the immune cell function assay for all other indications** as a **non-covered** benefit and as **investigational.**

Effective for dates of service on or after October 26, 2009:
Blue Advantage will treat **use of the immune cell function assay** to monitor and predict immune function **after solid organ transplantation** as a **non-covered** benefit and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This policy been updated regularly with searches of the MEDLINE database. The most recent literature search was performed through October 27, 2017.

Evidence reviews 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. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

The immune cell function assays are generally not meant to diagnose a condition (infection or rejection) that is concurrently present or absent, but to predict future risk of infection or

rejection. Thus although many studies evaluate 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). Immune function assays are risk-stratification tools rather than diagnostic tests. Risk stratification can result in improved health outcomes if specific clinical interventions based the results of the test decrease the risk of a poor health outcome, and the clinical intervention requires the result of the test.

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 immune function testing versus without immune function testing would provide robust evidence of clinical utility. Lacking such trials, clinical utility might be inferred by a strong chain of indirect evidence 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.

Immune Cell Function

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does use of immune cell function assays improve health outcomes in individuals who have received solid organ or hematopoetic cell transplants?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population(s) of interest are individuals who have a solid organ transplant or a hematopoietic cell transplant.

Interventions

The relevant interventions(s) of interest are immune cell function testing with ImmuKnow® or Pleximmune™.

Comparators

The relevant comparators of interest are standard monitoring of immunosuppression for those who have solid organ transplants and standard of care for those with hematopoietic cell transplantations.

Outcomes

The primary outcomes of interest are acute and chronic rejection episodes, graft dysfunction, graft survival, morbidity associated with graft dysfunction and overall survival posttransplant.

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

Setting
Patients are followed in posttransplant clinic following solid organ or hematopoetic cell transplant.

Immuknow® Test
Analytic Validity of Immuknow
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity of ImmuKnow®
Solid Organ Transplants
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. They tend to show that test results are correlated 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 to be a diagnostic tool but a risk-stratification tool. Systematic reviews of ImmuKnow® are first summarized, followed by individual studies of transplantation organized by transplant type, and then individual studies of hematopoietic stem cell transplantation.

Systematic Reviews
Ling et al. performed a systematic review and meta-analysis of studies published to July 2011 to assess the efficacy of ImmuKnow® assay in identifying risks of infection and rejection in adult transplant recipients. Nine studies published between 2008 and 2011 met the inclusion criteria. The meta-analysis of these nine studies incorporated 2,458 samples from transplant recipients, with 172 samples from patients with infection and 135 samples from patients with rejection. Three studies were among liver transplant recipients, three among kidney recipients, and one study each among heart, lung, and mixed organ recipients, respectively. The pooled estimates for the performance characteristics of the ImmuKnow® assay in identification of infection risk were a sensitivity of 0.58 (95% confidence interval [CI]: 0.52-0.64), a specificity of 0.69 (95% CI: 0.66-0.70), a positive likelihood ratio of 2.37 (95% CI: 1.90-2.94), a negative likelihood ratio of 0.39 (95% CI: 0.16-0.70), and a diagnostic odds ratio of 7.41 (95% CI: 3.36-16.34). The pooled estimates for ImmuKnow® assay in identifying risk of rejection were a sensitivity of 0.43 (95% CI: 0.34-0.52), a specificity of 0.75 (95% CI: 0.72-0.78), a positive likelihood ratio of 1.30 (95% CI: 0.74-2.28), a negative likelihood ratio of 0.96 (95% CI: 0.85-1.07), and a diagnostic odds ratio of 1.19 (95% CI: 0.65-2.20). Due to significant heterogeneity across studies, the review authors also conducted subgroup analyses in both liver and renal transplant patients. The subgroup analysis showed that the liver transplantation group had a relatively high pooled sensitivity of 0.85 and the renal transplantation group had a specificity of 0.80, indicating that the

different types of organ transplants may be one source of this observed heterogeneity; however, the positive likelihood ratio of the liver group was low and the negative likelihood ratio of the renal group was high, suggesting that it may be inappropriate to use the assay result to identify the risk of infections in either liver or renal transplant recipients. Based on the overall findings, the current evidence suggests that ImmuKnow® assay does not have sufficient diagnostic accuracy to identify individuals at risk of infection or rejection. In particular, the sensitivity is low, and the likelihood ratios that are close to 1.0 indicate that this test does not alter the probability of the specified outcomes to a large degree.

Rodrigo et al conducted a meta-analysis to identify studies (published to March 2012) documenting the use of ImmuKnow® assay to monitor immune function in adult liver transplant recipients. The authors identified five studies to analyze ImmuKnow® assay performance in infection and five studies in acute rejection. Two (of five) studies were also included in the above systematic review by Ling et al. The studies included a total of 651 cases in the infection meta-analysis and 543 cases in the acute rejection meta-analysis. Pooled sensitivity, specificity, positive likelihood ratio, diagnostic odds ratio and area under a summary receiver operating characteristic curve for infection were 0.84 (95% CI: 0.78-0.88), 0.75 (95% CI: 0.71-0.79), 3.3 (95% CI: 2.8-4.0), 14.6 (95% CI: 9.6-22.3), and 0.824 ± 0.034, respectively. The pooled estimates for acute rejection were 0.66 (95% CI: 0.55-0.75), 0.80 (95% CI: 0.76-0.84), 3.4 (95% CI: 2.4-4.7), 8.8 (95% CI: 3.1-24.8) and 0.835 ± 0.060, respectively. Heterogeneity was low for infection and high for acute rejection studies. Based on these findings, the ImmuKnow® assay could be considered a valid tool to know the risk of further infection in adult liver transplant recipients. However, due to significant heterogeneity across studies, conclusions about prediction of rejection risk with ImmuKnow® are limited.

Pediatric Transplantation

Several studies found no correlation between adenosine triphosphate (ATP) levels as determined by the ImmuKnow® assay and outcomes in cardiac transplant recipients. Rossano et al. studied 83 pediatric patients (median age, 4.9 years) undergoing heart transplant. ImmuKnow® assays were performed at routine follow-up visits from three months to more than five 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 ATP levels as measured by ImmuKnow® assay 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. As noted, however, it may be that pediatric patients' risks for post-transplant infection and rejection correspond to different ATP levels. Subsequent retrospective studies by Wong et al, Ryan et al, and Wozniak et al found no association between ATP production and outcomes in pediatric recipients of heart, kidney, or intestinal transplantations, respectively. Ryan et al observed a positive correlation between total peripheral white blood cell (WBC) count and ATP production ($r=0.28$, $p=0.04$) and suggested that proportion of activated T cells within submitted samples may provide more useful information.

Kidney Transplantation

Torío et al 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

one 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). Healthy blood donors served as controls (n=108). Immunosuppressive regimens included pre-transplant 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). No difference was observed between the rejection group (332.5 [131.7] ng/mL) and the stable group or the control group ($p>0.05$ for both comparisons).

Two retrospective studies of kidney transplant recipients found statistically significant correlations between ATP production and WBC. In a 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. In this study, ATP levels in five patients who developed viral infections in the early post-transplantation period (<50 days) were within normal limits. Methodologic limitations prevented any conclusion about the association of ATP levels with infections in eight patients in the late post-transplantation period (>120 days). In a study of 306 patients at a single U.S. center, Sageshima et al (2014) reported a correlation coefficients (R^2) of 0.264 ($p<0.001$) for the association between ATP production and WBC. In this study, mean (SE) ATP production in patients with biopsy-proven rejection (389 [56] ng/ml) and borderline/clinical rejection (254 [41] mg/mL) were not statistically higher compared with ATP production in patients without rejection (not reported). Mean (SE) ATP production in patients with opportunistic (349 [48] ng/mL) and other (345 [27] ng/mL) infections were not statistically lower compared with ATP production in patients without infection (not reported).

Reinsmoen et al studied 126 kidney transplant recipients to determine whether pretransplant immune parameters (ATP level, as well as 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. The mean pretransplant ATP level of recipients who had no clinical reason for a biopsy was significantly different from that of recipients who had biopsy-proven acute rejection at any post-transplant time point up to 36 months (285.3 +/- 143.2 vs. 414.3 +/- 138.5ng/mL, respectively). Recipients who underwent biopsy but had no diagnosis of acute cellular or antibody-mediated rejection had an intermediate mean value of 333.7 +/- 156.3 ng/ml. Pretransplant ATP levels were also significantly higher for recipients with early (less than 90 days) unstable creatinine levels, a significant predictor of early acute rejection, than for recipients with stable creatinine values (362.8 +/- 141.2 vs. 283.4 +/- 146.4 ng/mL, respectively). Post hoc analysis using a cutoff ATP level 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% confidence interval [CI]: 1.195, 11.201). The immune parameters were not used to guide modifications of the immunosuppression protocol. Graft survival and incidence of infection were not reported in this study.

Serban et al assessed ImmuKnow® assay results in 76 kidney transplant patients (mean age, 50 years) receiving antithymocyte globulin induction and maintenance immunosuppression. ATP

values were assigned to episodes of infection or rejection only if the ImmuKnow® measurement was performed within the 30 days preceding the adverse event. Over a median of 10 months of follow-up, there was a statistically significant difference between ATP activity measured in 15 of 18 patients with infection requiring hospitalization (median approximately 110 ng/mL) and 44 stable patients (median, approximately 220 ng/mL; p=0.002). The median ATP value of 9 of 11 patients with rejection (230ng/mL) was not significantly different from that observed in stable patients (p value not reported). The results of 3 patients whose blood was sampled for ImmuKnow® assay are unknown. ATP activity did not correlate with the number of CD4+ T-cells during the first 5 months post-transplant (r: 0.129; p=0.153) but did correlate with the number of neutrophils and total white blood cells within the first 3 months post-transplant (r>0.4; p<0.001). Because of substantial myeloid cell contamination of cells captured by the ImmuKnow® assay in patients with low CD4+ T-cell counts, the authors conclude that cells of the myeloid lineage substantially contributed to the ATP signal measured by ImmuKnow in these patients. Among 31 patients treated with darbepoetin, an erythropoiesis-stimulating agent often used in renal transplant recipients for the treatment of anemia, the median ATP value within the first two months post-transplant was approximately 260 ng/mL compared to 160 ng/mL in 38 patients who did not receive darbepoetin (p=0.017). There was no association between ATP values and development of rejection or infection at any time during the entire 10-month follow-up. The authors suggest that, in darbepoetin-treated patients, increased ATP activity is due to myeloid cell mobilization induced by darbepoetin rather than T-cell activation and does not justify increased immunosuppression. The relationship between ImmuKnow® results and infections was further analyzed using the ROC analysis. The area under the ROC curve (AUC) was 0.736, indicating a "fair" accuracy level of ImmuKnow® results for prediction of infection risk. The ATP cutoff value calculated based on the ROC curve was 165ng/mL, and the corresponding positive and negative predictive values were 0.513 and 0.874, respectively. This cutoff value for increased risk of infection differs from the manufacturer's cutoff value of 225 ng/mL However, because of the specific effects of antithymocyte globulin induction, the results of this study cannot be extrapolated to transplant recipients receiving no induction therapy or receiving induction agents that do not cause vigorous lymphocyte depletion (e.g., alemtuzumab, an anti-CD25 monoclonal antibody).

Zhou et al grouped 259 Chinese kidney transplant recipients (mean age, 38.8 ± 12.3 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 seven days before or after assay without antirejection therapy; n=16), or methylprednisolone (intravenous methylprednisolone given to treat biopsy-proven acute rejection within three days before or after assay; n=33). Post-transplant immunosuppressive regimens included corticosteroids, calcineurin inhibitors, and mycophenolate mofetil. Median ATP levels in the infection group (116.4 ng/mL, range 66.3–169.2) and the methylprednisolone group (182.3 ng/mL, range 113.6–388.8) were lower than in the stable group (347.7 ng/mL, range 297.9–411.7,p<0.001 for both comparisons). Median ATP levels in the rejection group were higher than in the stable group (615.9 ng/mL, range 548.8–743.5, p<0.001). The ROC analysis was also evaluated to determine optimal ATP cutoff values for infection and rejection in this sample. With an ATP cutoff value for infection of 238 ng/mL, sensitivity and specificity were 92.9% and 100%, respectively (AUC=0.991). For rejection, a

cutoff value of 497 ng/mL maximized sensitivity and specificity at 91.5% and 93.8%, respectively (AUC=0.988).

Huskey et al conducted a single-center, retrospective analysis to assess the predictive ability of ImmuKnow® to identify kidney transplant recipients at risk for opportunistic infection or acute rejection when used in routine clinical management. ImmuKnow® assay results were categorized according to the manufacturer's ATP cutoff values and correlated with subsequent infection or rejection occurring within 90 days after the assay. Patients matched for age, gender, and time of testing post-transplant who had neither infection nor rejection served as controls. Immunosuppressive regimens included prednisone, calcineurin inhibitors, and mycophenolate mofetil. Eighty percent of patients received pre-transplant antithymocyte globulin. Standard CMV and *Pneumocystis carnii* prophylaxis was administered. Ninety-four ImmuKnow® assays were performed in 85 patients with subsequent opportunistic infection and in matched controls. Mean ATP levels did not differ between cases (386 ng/mL) and controls (417 ng/mL; p=0.24). A low ATP level (≤225 ng/mL) was not associated with an increased risk of infection (OR: 1.34, 95% CI: 0.64, 2.82, p=0.43). Forty-seven ImmuKnow® assays were performed in 47 patients with subsequent acute rejection and in matched controls. Mean ATP levels did not differ between cases (390 ng/mL) and controls (432 ng/mL; p=0.25). A high ATP level (≥525 ng/mL) was not associated with an increased risk of rejection (OR 1.87, 95% CI: 0.47, 8.38, p=0.48).

Subsequent studies in kidney transplant recipients have demonstrated no association between ATP production and risk of acute rejection or viral infections using manufacturer-recommended cutoffs for ImmuKnow® or have suggested an alternative approach to determining optimal cutoff values. In a prospective cohort study of 55 patients followed for three years, Libri et al (2014) observed that ATP production was often lower in patients with acute rejection compared with patients without acute rejection, and was often greater in patients with infection compared with patients without infection. Using labelled cutoffs for ImmuKnow®, AUC was 0.44 (95% CI, 0.18 to 0.71) for acute rejection and 0.37 (95% CI, 0.22 to 0.53) for viral or major respiratory tract infections. In a 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). The cutoff used for this analysis was 300ng/mL. To optimize ImmuKnow® performance, Quaglia et al (2014) and Wang et al (2014) both proposed assessing change in ATP production over time, rather than single values. In a retrospective study of 118 patients, Quaglia et al reported 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 one to month three. In a prospective study of 140 patients, Wang et al reported 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.

Heart Transplantation

Three studies have examined ATP production in adult heart transplant recipients. Gupta et al studied 125 adult heart transplant recipients, the majority of whom underwent ImmuKnow assay testing more than 1 year post-transplant. There was no apparent correlation between ATP level and rejection (n=3). For 7 patients who developed infection, the median ATP level was 267 ng/mL and did not differ from the median ATP level in 104 patients who did not develop infection (282 ng/mL). There was a significant correlation between ATP level and white blood

cell count but not between ATP level and absolute lymphocyte count, suggesting that non-lymphocytes also may influence the ATP response. This idea is supported by a 1994 study of CD4+ T-cell responsiveness to three stimulants (including phytohemagglutinin) in HIV-positive patients. The authors suggest that assays performed in clinical laboratories should profile immunoregulatory cytokines (e.g., interleukin-2), which modulate the complex interplay between cellular and humoral immune mechanisms.

Israeli et al correlated ImmuKnow® assay results with clinical status in 50 immunosuppressed heart transplant recipients (median age 58.5 years). The median ATP value of 280 blood samples collected from patients during clinical quiescence (i.e., good clinical status with normal heart function) was 351ng/mL. ATP values were within the manufacturer's "moderate" range of immune function (225-525 ng/mL) in 176 (63%) of these samples. The median ATP value of 22 blood samples collected during episodes of biopsy-proven acute rejection was 619 ng/mL, a statistically significant difference ($p<0.05$). The median ATP value of 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 value during clinical quiescence ($p<0.05$). While these ATP values fall within the manufacturer's defined ranges for increased risk of infection (<225 ng/mL) and increased risk of rejection (>525 ng/mL), the blood samples were drawn during the adverse event rather than before, making it uncertain whether the ImmuKnow® results were predictive of the adverse event.

A retrospective study by Kobashigawa et al correlated ImmuKnow® assay results from 296 adult heart transplant recipients (mean age 54.6 ± 12.8 years) with infection or rejection episodes occurring within one month of assay. Assays were performed between two weeks and ten 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. Heart 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 ATP level was lower in patients with infection (187 ± 126 ng/mL) than in controls (280 ± 126 ng/mL, $p<0.001$). Ten percent of ATP levels less than 200 ng/mL were associated with infection, and 2% of ATP levels greater than 200 ng/mL were associated with infection ($p<0.001$). Mean ATP levels did not differ between patients who developed rejection (327 ± 175 ng/mL) and controls ($p=0.35$). The 200 ng/mL cutoff was chosen based on ROC analysis to maximize sensitivity (71%) and specificity (73%; AUC=0.728). Although limited by its retrospective design, this study suggested that ImmuKnow might be associated with prediction of infection, not with transplant rejection, in heart transplant patients.

Liver Transplantation

Cabrera et al assessed the ability of the ImmuKnow® assay to differentiate between acute cellular rejection (ACR) and recurrent hepatitis C in 42 adult patients who had hepatitis C virus (HCV)-related end-stage liver disease. 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 polymerase chain reaction (PCR), was not used to

diagnose HCV. The ImmuKnow® assay was performed with blood collected prior to biopsy, and biopsy samples were interpreted by histopathologists blinded to the results of the ImmuKnow® assay. The median ATP value in 12 patients diagnosed with ACR was 283.3 (range: 241.1-423.0), and the median ATP value in 15 patients diagnosed with recurrent HCV was 148.0 (range 33.7-186.0), a statistically significant difference ($p<0.001$). The median ATP value in 15 patients with mixed biopsy features of both ACR and recurrent HCV, but predominance of neither, was 234.0 (range: 155.3-325.0), a statistically significant difference from both the ACR group ($p=0.02$) and the recurrent HCV group ($p<0.001$). Of note, while 100% of patients with recurrent HCV had ATP values within the manufacturer's range for increased risk of infection (<225 ng/mL), 100% of patients with ACR had ATP values outside of the manufacturer's cutoff for increased risk of rejection (>525 ng/mL).

To assess the ImmuKnow® assay's ability to differentiate acute cellular rejection from recurrent HCV infection among patients transplanted for HCV-related liver disease, Hashimoto et al. (18) conducted a retrospective review of 54 allograft liver transplant recipients who had concomitant ImmuKnow® assay results available (mean age 52 years, range 40-63). Liver biopsies were performed every six months after liver transplantation and when clinically indicated due to elevated liver function tests. Biopsies were read by a pathologist who was blinded to ImmuKnow® assay 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 four groups based on biopsy findings: acute cellular rejection (n=11), recurrent HCV (n=26), normal biopsy (n=12), and overlapping features of both acute cellular rejection and recurrent HCV. The mean ATP level in acute cellular rejection (365 ± 130 ng/mL, range 210-666) was higher than in normal biopsy (240 ± 71 ng/mL, range 142-387; $p=0.006$). The mean ATP level in recurrent HCV (152 ± 100 ng/mL, range 20-487) was lower than in both acute cellular rejection ($p<0.001$) and normal biopsy ($p=0.019$). The mean ATP level of patients with overlapping features of both acute cellular rejection and recurrent HCV (157 ± 130ng/mL, range 25–355) did not differ from the other groups. Seventy-three percent of patients with acute cellular rejection had ATP levels in the manufacturer-defined moderate range. Eighty-eight percent of patients with recurrent HCV had ATP levels in the low range ($p<0.001$). ROC analysis yielded a cutoff level of 220ng/mL with sensitivity of 88.5% and specificity of 90.9% (AUC=0.93, 95% CI: 0.85, 1.00).

Cheng et al evaluated the ability of the ImmuKnow® assay to predict recurrence of hepatocellular carcinoma (HCC) in Chinese patients undergoing liver transplantation for HCC. A threshold ATP level of 175 ng/mL was initially determined from 176 assays of 60 patients with HCC (mean age 49.8 ± 8.7 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 ATP levels in patients with recurrent HCC (137.8 ± 66.4 ng/mL) were lower than in those without recurrence (289.2 ± 133.9 ng/mL, $p<0.01$). Sensitivity and specificity for the 175 ng/mL threshold value were 83.3% and 83.6% respectively (AUC=0.869). ImmuKnow® was then administered to a second cohort of 92 patients with HCC undergoing liver transplantation (mean age 50.1 ± 10.3 years). Patients were stratified by high immune response (mean ATP level >175 ng/mL) and low immune response (mean ATP level ≤175 ng/mL). Seventeen of 73 patients (23.3%) in the high response group and 16 of 19 patients (84.2%) in the low response group developed HCC recurrence ($p<0.001$). Mean ATP levels 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 (OR 7.28, 95% CI: 3.23, 16.13) but not overall survival (OR 2.20, 95% CI: 0.56, 8.65). This study also correlated ImmuKnow® assay results with clinical status (infection or rejection) among a cohort of the original 60 patients with HCC plus 45 additional patients with non-malignant 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 two 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 ATP levels during infection (145.2 ± 87.0 ng/mL) and rejection (418.9 ± 169.5 ng/mL) differed from the mean level during stability (286.6 ± 143.9 ng/mL, p<0.01 for both comparisons). ROC analysis showed that the optimum cutoff ATP value for infection was 200 ng/mL with sensitivity of 79.2% and specificity of 75.0% (AUC=0.842). The cutoff value for rejection was 304 ng/mL with sensitivity of 79.6% and specificity of 76.4% (AUC=0.806). Another retrospective study of 87 liver transplant recipients utilized a cutoff level for rejection of 407 ng/mL based on ROC analysis with sensitivity and specificity of 85.7% and 80.9%, respectively (AUC=0.869).

An additional study reported on the correlation between ImmuKnow values with immunosuppression in liver transplant recipients.

Lung Transplantation
Piloni et al (2016) reported on a retrospective cohort study evaluating the association between over- (ImmuKnow score, corresponding to intracellular ATP, ≤226 ng/mL) vs. adequate or under-immunosuppression (ImmuKnow score > 226 ng/mL) in a sample of 61 patients undergoing follow up for lung transplantation. ImmuKnow testing had been performed at 6 month follow up for the 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 over- immunosuppression. Being in the over- immunosuppression 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=0.0030. However, given that many patients tested in the as-needed group may have been tested because of suspected over- immunosuppression, the risk of bias is very high.

Bhorade et al (2008) assessed the relationship between low posttransplant ATP production (≤225 ng/mL) and recent infection in 57 immunosuppressed adult lung transplant recipients. 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, cytomegalovirus [CMV] infection); 14 of these (93%) had ATP production <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%). Without comparing postinfection ATP production with preinfection ATP production, it is not possible to draw conclusions about whether low ATP production contributed to or resulted from the development of infection. In a 2013 U.S. single-center study on 175 adult lung transplant recipients, Shino et al reported that ImmuKnow® had some predictive ability but was unlikely to be sufficiently

accurate for use in clinical care. AUC was relatively low at 0.61. At a cutoff of 525 ng/mL, there was a significant increase in the risk for acute cellular rejection (OR, 2.1; 95% CI, 1.1 to 3.8). However, at this cutoff, sensitivity was 35%, with specificity of 82%. When a cutoff of 425ng/mL was used, sensitivity was 53%, and specificity was 65%.

Husain et al assessed the correlation of ImmuKnow assay results to different types of infections (bacterial, fungal, viral) in 175 adult lung transplant recipients receiving immunosuppression induction with alemtuzumab. Blood samples were collected prospectively as a part of routine surveillance in all patients during 2 to 48 months of follow-up. Periods of stability were defined as no infection occurring one month before or after the blood draw. For infectious episodes, only ATP values drawn within one month before the episode were analyzed. The median ATP value during stability was 174.8ng/mL (25th–75th percentile, 97–306 ng/mL). Significantly lower median ATP values were seen in 13 cytomegalovirus (CMV) infections (49.3 ng/mL, $p<0.001$), 5 infections with other viruses, and 14 bacterial pneumonias (92.4 ng/mL, $p=0.002$). The median ATP value in fungal disease (85ng/mL) did not differ significantly from that in stability (p-value not reported). Four patients who developed invasive pulmonary aspergillosis all had ATP values less than 50 ng/ml. Generalized estimating equation (GEE) logistic regression analysis demonstrated an odds ratio (OR) of 2.81 (95% CI: 1.48, 4.98) for increased risk of infection with ATP values less than 100 ng/mL and an OR of 9 (95% CI not reported) with values less than 50 ng/mL. In comparison, a diagnosis of cystic fibrosis yielded an OR of 2.66 (95% CI: 1.26, 5.63) and CMV mismatch (donor positive, recipient negative) yielded an OR of 2.97 (95% CI: 1.52, 5.80). Note that all ImmuKnow® values, both during periods of stability and within the month before infectious episodes, fall below the manufacturer's cutoff for increased risk of infection (225ng/mL).

Section Summary: Clinical Validity for Solid Organ Transplants

Across all the studies among various types of solid organ transplants, ImmuKnow levels have been 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 heterogeneity across studies. The timing of the test in relation to the observed outcomes and whether the test was routine or performed for suspected infection or rejection affect test performance characteristics. In many cases, the threshold values were declared after the study. Validation of the threshold values with external validation samples is needed. It cannot be determined from these studies whether the discrimination of risk is clinically important, and whether there is compelling chain of logic that treatment modifications based on predicted risk would improve patient outcomes.

Hematopoietic Cell Transplantation (HCT)

Two studies examined the role of ImmuKnow® in hematopoietic cell transplantation (HCT), one in autologous transplants and one in allogeneic transplants. Manga et al assessed ATP levels in 16 adult patients (mean age 52 years) with hematologic malignancies (multiple myeloma, B- or T-cell lymphoma, and acute myeloid leukemia) undergoing mobilization with granulocyte-colony stimulating factor (G-CSF) with or without granulocyte-macrophage-colony stimulating factor (GM-CSF) for autologous HCT. Mean ATP level on day five of G-CSF therapy in ten patients who survived more than two years after mobilization (673 ± 274 ng/mL) was higher than in five patients who died within two years (282 ± 194; $p=0.014$). ROC analysis identified an

ATP cutoff value of 522 ng/mL for predicting patient survival with sensitivity and specificity of 0.8 and 1.0, respectively (AUC=0.880). Gesundheit et al examined 170 ATP levels collected from 40 patients (median age 34 years, range 3-64) following engraftment of allogeneic HCT for various malignant (acute and chronic myeloid leukemia, acute and chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome, and ovarian, breast, and testicular cancer) and non-malignant (severe aplastic anemia, thalassemia major, and adrenoleukodystrophy) diseases. ImmuKnow® assay results were categorized "low" or "normal" according to the manufacturer's ATP cutoff values and correlated with post-engraftment clinical course. Overall survival for the immunocompetent ("normal") group was 83% (10 out of 12 patients) at 13 months of follow-up. Overall survival for the immunocompromised ("low") group was 12% (3 out of 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.

Section Summary: Clinical Validity for Hematopoietic Cell Transplants

Two studies evaluated the association between ImmuKnow and prognosis in hematopoietic cell transplantation. 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 compelling chain of evidence that treatment modifications based on predicted risk would improve patient outcomes.

Clinical Utility of ImmuKnow

Solid Organ Transplant

Liver Transplantation

The only study that could be identified comparing patients managed with and without immune response assays was a 2015 study by Ravaioli et al. 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 where reduced 25% when ImmuKnow values were less than 130, and increased by 25% when ImmuKnow values were greater than 450. In the control group, ImmuKnow testing was performed but not revealed to treating physicians, and tacrolimus was managed according to standard practice. The declared outcomes of the study were survival, infection rate, rejection rate, and graft loss. One-year survival was 95% in the ImmuKnow group and 82% in the control group ($p< 0.01$). Of the 33 deaths, 11 were caused by infection (distribution of the 11 deaths by treatment group not reported). Patients in the control group were reported to have had higher bacterial and fungal infection rates but the numbers reported in the article included errors and are inconsistent. There were no differences in rejection events between the ImmuKnow group and the control group. Although the study showed a 10% absolute benefit in mortality, there are concerns about study validity. The standard of care monitoring practice is not described. The study was performed at a single center. The control mortality rate may not be representative of modern liver transplant outcomes. The difference in mortality rate seems implausibly large given the known characteristics of ImmuKnow in discriminating risk of infection. Although the study is suggestive of a benefit of monitoring immunosuppression with ImmuKnow in liver transplant patients, many trial shortcomings suggest it needs to be replicated.

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

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. However, the absolute risk and increments of risk are uncertain because of 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.

Section Summary: ImmuKnow Test for Hematopoietic Cell Transplants
For hematopoietic cell transplants, 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™
Analytic Validity of Pleximmune™
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinical Validity of Pleximmune™
The Food and Drug Administration documents have described a clinical validation study of Pleximmune. Among a sample of 33 pretransplant patients, Pleximmune™ had 57% sensitivity and 89% specificity for identifying rejection. Among a sample of 64 posttransplant patients, Pleximmune™ had 84% sensitivity and 80% specificity for identifying rejection. Almost no details were provided on study validation. A study by Ashokkumar et al evaluated the association between CD154 expression and rejection among pediatric liver transplant patients. It is difficult to determine if the measure of CD154 expression used in this study is the same as the Pleximmune™ test. Using a different threshold value of Immunoreactivity Index (IR) than the current test, IR was associated with the risk of rejection.

A 2017 study by Ashokkumar et al reported on the preclinical development and validation of an allospecific CD154+ T-cytotoxic memory cell (CD154+ TcM) test to predict acute cellular rejection after liver or intestine transplantation in patients with pediatric liver or lung transplantation.37 Pleximmune was involved in the study design and assay standardization. A total of 127 patients (120 analyzable samples) were included in the training set (enrolled from 2006 to 2010) and 87 patients (72 analyzable samples) e 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 for difference between groups for all subjects 0.007). The immunoreactivity index (IR) was defined as the ratio of the reaction of donor-induced CD154+TcM to the reaction exceed those induced by reference peripheral blood leukocytes (PBL); 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 receiver operating characteristic (ROC) curve of 0.878 in the test set (0.791 in the validation set), while an IR of 1.23 pretransplant or greater was an associated with an ROC of 0.82 in the training set (0.842 in the validation set). The association test performance characteristics are shown in table 1.

Table 1. Test Performance Characteristics in Ashokkumar et al (2016)

Cutpoint	Performance Measures	Measures	95%
Posttransplant IR: 1.1	Sensitivity	84%	60%-96%
	Specificity	80%	65%-90%
	PPV	64%	43%-81%
	NPV	92%	78%-98%
Pretransplant IR: 1.23	Sensitivity	57%	30%-81%
	Specificity	89%	65%-98%
	PPV	80%	44%-96%
	NPV	74%	51%-89%

CI: confidence interval; IR: immunoreactivity index; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio.

Clinical Utility of Pleximmune™

We did not identify any studies directly demonstrating improved patient outcomes. An argument for clinical utility by 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 solid organ transplants and HCTs.

Section Summary: Pleximmune Test for Solid Organ Transplants

For the use of the Pleximmune test in the solid organ transplant population, extremely limited evidence is available and includes a study with a small number of patients described briefly in the Food and Drug Administration 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.

Section Summary: Pleximmune Test for Hematopoietic Cell Transplants

No evidence for the clinical validity or clinical utility of the Pleximmune test for hematopoietic cell transplant populations was identified.

Summary of Evidence

For individuals who have a solid organ transplant or hematopoietic cell transplant who receive testing using an immune cell function assay 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, test accuracy, 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 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 the effects of the technology on health outcomes.

For individuals who have a solid organ transplant or hematopoietic cell transplant who receive testing using an immune cell function assay with Pleximmune, the evidence includes the U.S. Food and Drug Administration documentation and a report on the test's development and validation. Relevant outcomes are overall survival, test accuracy, 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 Food and Drug Administration 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 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 the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

Transplantation Society

The International Cytomegalovirus (CMV) Consensus Group of the Transplantation Society published an international consensus statement on the management of CMV in solid organ transplant in 2010. The authors state that "there are no clinical studies demonstrating that management decisions based on immunologic monitoring affect patient outcomes." Routine immunologic monitoring is not recommended.

International Society of Heart and Lung Transplantation

Guidelines for the care of heart transplant recipients published in 2010 by The International Society of Heart and Lung Transplantation do not include ImmuKnow®.

American Society of Transplantation

In 2006, the AST published recommendations for the screening, monitoring, and reporting of infectious complications in immunosuppression trials of organ transplant recipients. These recommendations define relevant infectious complications to be included in the reporting of immunosuppression trials and recommend specific laboratory monitoring and surveillance methods. The immune cell function assay is not included in these recommendations.

Guidelines on Use of Assays for Monitoring Autophagy in Higher Eukaryotes
Guideline updates published in 2016 by Klionsky et al discussed a number of assays in the context of monitoring autophagy, concluding that the best approach would be to use a combination of several assays, as opposed to a single test. The guidelines did not address the topic specific to this evidence review (monitoring of immunosuppression in the context of transplant); they also made no mention of ImmuKnow or Pleximmune in their recommendations.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:
Cylex, ImmuKnow®, ImmuKnow® assay, Immune Cell Function Assay, Transplantation Immune Cell Function Assay, Pleximmune™

Approved by Governing Bodies:
In April 2002, ImmuKnow® (Cylex, acquired by ViraCor-IBT Laboratories, Lee's Summit, MO), an immune cell function assay, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. 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 FDA through the 510(k) process. The FDA-indicated use of the Immune Cell Function Assay is for the detection of CMI in an immunosuppressed population. In 2010, a device modification for this assay was cleared for marketing by FDA through the 510(k). There were no changes to the indications or intended use.

In August 2014, Pleximmune™ (Plexision, Pittsburgh, PA) was approved by FDA through the humanitarian device exemption process. The test is intended for use in the pretransplantation and early and late posttransplantation period in pediatric liver and small bowel transplant patients for the purpose of predicting the risk of transplant rejection within 60 days after transplantation or 60 days after sampling.

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:
CPT Codes:

86352	Cellular function assay involving stimulation (e.g., mitogen or antigen) and detection of biomarker (e.g., ATP)

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