Anthem

Medical Policy

Subject: Immune Cell Function Assay
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Description/Scope

This document addresses cellular function assays including the ImmuKnow® assay (Viracor-IBT Laboratories, Inc., Lee's Summit, MO), CU Index® (Viracor-IBT Laboratories, Inc., Lee's Summit, MO), Pleximark™ (Plexision, Inc., Pittsburg, PA), Pleximmune™ (Plexision, Inc., Pittsburg, PA) and CMV inSIGHT™ T Cell Immunity Panel (Eurofins Viracor Inc., Lenexa, KS). Immune cell function assays have been developed for use in the detection of changes in cell mediated immunity (CMI) in individuals undergoing immunosuppressive therapy following solid organ transplant and individuals undergoing treatment for a variety of other conditions such as chronic urticaria, Lyme disease, autologous and allogeneic hematopoietic stem-cell transplant recipients, immunodeficiency disorders and immune-mediated diseases such as multiple sclerosis and rheumatoid arthritis (RA).

Position Statement

Investigational and Not Medically Necessary:

An immune cell function assay is considered **investigational and not medically necessary** for all indications including, but not limited to:

1. Management of solid organ transplant rejection in an individual undergoing immunosuppressive therapy;
2. Identification of risk for rejection prior to kidney or any other solid organ transplantation;
3. Management of autologous or allogeneic hematopoietic stem cell transplantation;
4. Management of immunodeficiency disorders including human immunodeficiency virus (HIV) and severe combined immunodeficiency disease (SCID) and immune mediated disorders including rheumatoid arthritis (RA) and multiple sclerosis;
5. Testing for urticaria;
6. Diagnosis and management of Lyme disease.

Rationale

Solid Organ Transplant Management

A challenge of transplant management is evaluating the effect of immunosuppressive therapy on the transplant recipient. Excessive immunosuppression may result in infection or drug toxicity, and insufficient immunosuppression may result in increased risk of organ rejection. An immune cell function assay, ImmuKnow, received clearance through the U.S. Food and Drug Administration's (FDA) 510(k) process for the detection of CMI response in those undergoing immunosuppressive therapy for solid organ transplant. This assay measures the concentration of adenosine triphosphate (ATP) released from circulating $CD4^+$ T cells following a 15-18 hour incubation of a peripheral blood sample with phytohemagglutinin (PHA), a global stimulator of the immune system.

Well-designed clinical trials that compare the clinical utility of immune cell function assays with conventional methods of determining immune functioning in transplant recipients are lacking. The majority of studies of immune cell function assays are prospective observational or retrospective studies that assess the correlation between adenosine triphosphate (ATP) levels with clinical outcomes to identify the risk of infection or disease in individuals who have undergone organ transplantation.

Kowalski and colleagues (2006) reported on a meta-analysis of 504 solid organ transplant recipients (heart, kidney, kidney-pancreas, liver and small bowel) from 10 U.S. centers in which the ImmuKnow assay was utilized. Data were collected prospectively during observational studies throughout the United States (U.S.) and combined with cross-sectional data used to support the FDA's clearance of the assay. Blood samples were taken from recipients at various times post-transplant and compared with clinical course (stable, rejection, infection). In this analysis, 39 biopsy-proven cellular rejections and 66 diagnosed infections occurred. Odds ratios of infection or rejection were calculated based on measured immune response values. Results demonstrated that a recipient with an immune response value of 25 ng/ml ATP was 12 times (95% confidence interval [CI], 4-36) more likely to develop an infection than a recipient with a stronger immune response. Similarly, a recipient with an immune response of 700 ng/ml ATP was 30 times (95% CI, 8-112) more likely to develop a cellular rejection than a recipient with a lower immune response value. The intersection of odds ratio curves for infection and rejection in the moderate immune response zone (280 ng/ml ATP) was noted. This intersection of risk curves provides an immunological target of immune function for solid organ recipients. The authors concluded ImmuKnow assay has a high negative predictive value and provides a target immunological response zone for minimizing risk and managing individuals to stability.

Huskey and colleagues (2010) noted that since the FDA review of the ImmuKnow assay, "few studies have clarified the value of the ImmuKnow assay in the clinical monitoring of patients after kidney transplant." Because many of these previous studies had a limited number of participants, the authors performed a large retrospective analysis of ImmuKnow results obtained over a 5-year period and compared those values with subsequent events of opportunistic infections (OI) and acute rejection (AR). A total of 1330 ImmuKnow assay values in 583 renal transplant recipients from a single institution from 2004 to 2009 were evaluated. The assay values of the transplant recipients were compared to that of a control population matched for time, post-transplantation, gender and age. In participants with OI (n=94) there were no differences in prior assay values compared to that of matched controls (386 versus 417 ng/ml, p=0.24). In 47 participants with AR, there were also no differences detected in prior assay results (390 versus 432 ng/ml, p=0.25) when compared with controls. "Low" values (less than or equal to 225 ng/ml) lacked sensitivity and specificity as a predictive test for subsequent OI, as did "strong" (greater than or equal to 525 ng/ml) values as a predictive test for subsequent AR. The authors concluded "ImmuKnow assay measures at a single time point did not identify individuals at risk for the future development of clinically significant events." They also noted that further studies are required to clarify the role of this test in immune monitoring of kidney transplant recipients.

Three meta-analyses (Ling, 2012; Rodrigo, 2012; Wang, 2014) have assessed the use of the ImmuKnow assay in solid organ transplant recipients. The first was conducted by Ling and colleagues (2012) who performed a meta-analysis and systematic review of studies published to July 2011 to evaluate the efficacy of ImmuKnow assay in identifying risks of infection and rejection in adult

transplant recipients. Nine studies published between 2008 and 2011 met inclusion criteria. The meta-analysis of these nine studies incorporated 2458 samples from transplant recipients, with 172 samples from individuals with infection and 135 samples from those with rejection. Three studies included liver transplant recipients, three included kidney recipients, and one study each for heart, lung, and mixed organ recipients. The pooled estimates for the performance characteristics of the ImmuKnow assay in identification of infection risk were a sensitivity of 0.58 (95% 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). Subgroup analyses were also conducted in both liver and renal transplant recipients due to significant heterogeneity across studies. The subgroup analysis showed that the liver transplant group had a relatively high pooled sensitivity of 0.85 and the renal transplant 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 evidence presented in this meta-analysis suggests that ImmuKnow assay does not have sufficient diagnostic accuracy to identify individuals at risk of infection or rejection. Additional studies are still needed to clarify the usefulness of this assay for identifying risks of infection and rejection in adult transplant recipients.

The second meta-analysis was conducted by Rodrigo and colleagues (2012) and included 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 the five studies were also included in the Ling 2012 review. 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. However, there was significant heterogeneity across studies, which prevented concluding that ImmuKnow assay identifies liver transplant recipients at risk for rejection.

The third meta-analysis conducted by Wang and colleagues (2014) included six studies representing a total of 1626 subjects. The aim of this study was to assess Immuknow's ability to predict and monitor the risk of infection and acute rejection following a renal transplant. Following extraction of data, the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were assessed. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio of ImmuKnow for predicting the risk of infection were 0.51 (95% CI, 0.45-0.57), 0.75 (95% CI, 0.71-0.78), 1.97 (95% CI, 0.91-4.26), 0.67 (95% CI, 0.38-1.19), and 3.56 (95% CI, 0.80-15.89), respectively. A diagnostic odds ratio of 13.81 (95% CI, 0.79-240.44), with a sensitivity of 0.51 (95% CI, 0.40-0.61), a specificity of 0.90 (95% CI, 0.87-0.93), a positive likelihood ratio of 4.45 (95% CI, 0.91-21.74), and a negative likelihood ratio of 0.35 (95% CI, 0.08-1.45), were found in the analysis of the predictive value for acute rejection. The authors concluded:

> Our analysis did not support the use of the ImmuKnow assay to predict or monitor the risks of infection and acute rejection in renal transplant recipients. Further studies are needed to confirm the relationships between the ImmuKnow assay and infection and acute rejection in kidney transplantation.

In 2015, Ravaioli and colleagues published results from a prospective, randomized clinical trial of ImmuKnow in which 202 individuals were randomly assigned to the control group (standard practice; n=102) or the interventional group (serial immune function testing; n=100). The serial testing in the interventional group was performed before transplant, immediately post-op, and at post-op day 1, weeks 1, 4, 6 and 8, and months 3, 6, 9 and 12. The authors reported that based on the study participants' immune scores, tacrolimus doses were adjusted either up or down by 25% based on pre-determined cut-off values. Survival at 1 year was significantly higher in the ImmuKnow arm compared to the control group (95% versus 82%; $p<0.01$) in participants with a MELD score > 20. Furthermore, the incidence of infections lasting longer than 14 days post-transplant was significantly lower among those in the ImmuKnow arm (42% versus 54.9 %; $p<0.05$). The difference in survival was attributed to significantly lower bacterial and fungal infections in the intervention arm. There are several weaknesses of this study that warrant consideration, such as the inconsistency in numbers of participants reported throughout the publication. The significance in overall survival at 12 months between the intervention group and control group is marginal ($p<0.05$; n=202); this is of particular concern given that the numbers reported in this outcome are one of the aforementioned inconsistencies. Additionally, while the sub-group analysis in those with MELD scores > 20 gives the impression that survival in those managed by ImmuKnow was strikingly effective ($p<0.01$), there is no data reported on the comparability between the two arms of this markedly smaller subgroup (n=99). As a result, the possibility of confounding variables influencing the apparent correlation between survival and ImmuKnow-led management amongst those with MELD scores > 20, cannot be ruled out. Furthermore, the study concludes that its findings confirm that ImmuKnow's clinical utility is in its ability to manage infections, bacterial infections being the most prevalent in the report (57.1%), but again inconsistencies are present in the numbers reported to have acquired bacterial infections during the study period and the significance of the difference between groups is also marginal ($p<0.05$). Given the weaknesses described, in conjunction with the manufacturer of ImmuKnow funding the data collection and manuscript preparation, additional studies demonstrating reproducibility of the study results are warranted.

Several prospective and retrospective studies have evaluated the immune function assay as a predictor of allograft rejection and infection in kidney transplantation (He, 2013; Martínez-Flores, 2014; Myslik, 2014; Nishikawa, 2014; Quaglia, 2014; Ryan, 2014; Sageshima, 2014); liver transplantation (Mizuno, 2013; Sindhi, 2016); heart transplantation (Wong, 2014) and intestinal transplantation (Wozniak, 2014). The majority of these studies demonstrated statistically significant differences in ATP levels among individuals who have undergone transplantation and exhibit signs of infection or rejection compared with individuals without signs of infection or rejection, individuals who were otherwise clinically stable, or healthy controls. However, the studies were characterized by several weaknesses, including the fact that none evaluated sensitivity, specificity, or diagnostic accuracy of the immune function assay to accurately predict which individuals are at high risk of infection or transplantation rejection.

Evidence is insufficient to conclude that individualized titration of immunosuppressive therapy based on the results of ImmuKnow results in improved clinical outcomes in individuals following solid organ transplant. The utility of the assay to identify individuals at risk for rejection prior to kidney or any other solid organ transplant or for the management of other conditions is currently unproven. The immune cell function test, ImmuKnow, has not demonstrated a net improvement in clinical outcomes for any indication. Additional well-designed studies with larger populations are needed to establish the reliability and utility of this assay as a prognostic tool. There are ongoing clinical trials further evaluating the clinical utility of ImmuKnow in transplant recipients.

The American Society of Transplantation (AST) (2006) does not include the use of the ImmuKnow assay in its publication: "Recommendations for Screening, Monitoring and Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation." Educational guidelines for the management of transplant recipients in the community setting and for infectious diseases in transplant recipients published in 2009 by AST also do not include ImmuKnow.

The International 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.

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

Use in Conditions other than Solid Organ Transplantation

Augustine and colleagues (2007) reported that individuals with T-cell immunodeficiency diseases, including SCID may have defective lymphocyte responses. They also noted that individuals with malignancies following bone marrow transplantation, with severe viral infections, or undergoing immunosuppressive therapy for other reasons, may have severe suppression of cell-mediated responses. The traditional “gold standard” method for testing cell-mediated immune function is the lymphocyte proliferation assay with incubation times varying from 4 to 6 days. The authors compared the lymphocyte proliferation assay with the ImmuKnow assay which has an overnight incubation period. Whole blood from 20 individuals suspected of having cell-mediated immunity defects and 21 normal controls were included in this study. Exact diagnoses of the individuals were not known because of Health Insurance Portability and Accountability Act (HIPAA) regulations but it was known that 1 individual had SCID. Of the 20 samples tested from individuals with suspected cell-mediated immunity defects, 9 (45%) exhibited normal responses in both assays and 7 samples (35%) had results considered as very low in both assays. There was agreement between both assays in 16 out of 20 (80%) of the individuals. Whole blood samples taken from the 21 normal controls were also tested using the ImmuKnow assay and the lymphocyte proliferation assay. A total of 20 (95%) of the 21 controls had results that agreed in both assays, and 19 (90%) of the controls had both normal proliferation and moderate to strong responses. Results from one individual with SCID demonstrated very low responses in both methods. The authors noted that the ImmuKnow assay may be a useful screening tool for more rapid detection of blood samples with decreased cell-mediated immune responses. However, they did not propose that it be utilized to replace the traditional method but to serve as a rapid 18-24 hour screen prior to the traditional 5 to 7 day proliferation assay. Study limitations include a limited sample size.

Gesundheit and colleagues (2010) studied immune monitoring post allogeneic hematopoietic stem cell transplant (alloHSCT). The authors noted “after alloHSCT, immunosuppressed patients are susceptible to opportunistic infections and uncontrolled function of the graft can result in graft versus host disease.” Between October 2005 and November 2007, a total of 170 blood samples were collected from 40 individuals post alloHSCT performed for various malignant (31) and nonmalignant (9) diseases and from 13 healthy controls. The ImmuKnow assay was utilized for $CD4^+$ ATP levels to compare known clinically immunocompromised versus immunocompetent participants after alloHSCT. The researchers also compared the reconstitution of white blood cell count to the ImmuKnow results and clinical status. The participants’ clinical course correlated with the stratification of immune response established by the ImmuKnow assay for solid organ transplantation (immunocompetent versus immunocompromised), and this sometimes differed from their white blood cell count. The authors concluded that the ImmuKnow assay should be evaluated prospectively in clinical trials.

Manga and colleagues (2010) reported on a study of 16 adults with hematologic malignancies undergoing hematopoietic stem cell (HSC) mobilization prior to autologous transplantation in which the ImmuKnow assay was used to measure ATP activity. Mobilization of HSC was achieved using hematopoietic growth factors (such as granulocyte colony stimulating factors [G-CSF]). The immune cell function assay measured the ATP activity in G-CSF treated individuals. The ATP activity was found to be significantly higher than that measured in healthy or “nonmobilized” individuals. The authors concluded that “the significance of ATP production by $CD4^+$ cells in individuals with hematologic malignancies should be investigated in larger studies.”

Akimoto and colleagues (2013) examined the ability of the ImmuKnow assay to predict the risk of infection in individuals with RA receiving disease-modifying anti-rheumatic drugs. The amount of ATP produced by $CD4^+$ cells in response to phytohemagglutinin was measured in 117 individuals with RA without infection and 17 individuals with both RA and infection. The results were compared to those obtained from 75 healthy controls. The mean ATP level was lower in individuals with infection compared to both healthy controls and those without infection. Also, the mean ATP level in individuals without infection was lower than that in healthy controls. No correlation was noted between the Disease Activity Score in 28 joints and the ATP level. The authors concluded that their results should be interpreted with caution because this was not a prospective study.

In 2021, Monforte conducted a prospective observational study to evaluate the prognostic value of ImmuKnow for predicting non-cytomegalovirus (CMV) infections in 92 lung transplant recipients. A total of 23 (25%) recipients developed non-CMV infections between 6 and 12 months post-transplant. The ImmuKnow demonstrated a sensitivity of 95.7%, specificity of 18.8%, positive predictive value (PPV) of 28.2%, and negative predictive value (NPV) of 92.9% (AUC 0.64; p=0.043). The study investigators conclude that the ImmuKnow®'s predictive value is poor for non-CMV infection.

In 2022, Maidman and colleagues published results of a retrospective observational study to determine the utility of ImmuKnow baseline values (pre-transplant) to predict the likelihood of rejection at the time of first biopsy after a cardiac transplant. A total of 81 study recipients had pre-transplant ImmuKnow results. Among the pre-transplant low ImmuKnow levels (n=15) group, detection of early rejection was virtually nil. In the moderate-high pre-transplant ImmuKnow group (n=66), 16 (24.2%) experienced early rejection (p=0.033). In this retrospective study of cardiac transplant recipients, low ImmuKnow levels pre-transplant were associated with a lower risk of early rejection relative to recipients with moderate or high levels pre-transplant. Further, prospective investigation with a more robust sample is warranted.

In 2023, Chen and colleagues conducted a retrospective analysis to evaluate an immune cell function assay and CD3 lymphocyte counts and their association with adverse outcomes post-pediatric orthotopic heart transplant (OHT). A total of 381 immune cell function assays and 493 CD3 laboratory values were analyzed from 78 pediatric subjects within 6 months post-OHT. There were 14 subjects treated for biopsy-proven acute rejection, 4 of whom had International Society for Heart and Lung Transplantation (ISHLT) grade 2R/3A rejection. There was at least one detectable cytomegalovirus or Epstein-Barr virus DNAemia in 26 subjects within the study timeframe. In subjects with viremia versus those without, CD3 and ICFA values were not significantly different. No association was found between the immune markers studied and adverse outcomes.

The ImmuKnow is being investigated in a number of other immune-mediated diseases, such as irritable bowel syndrome (IBS) and lupus, however even in pilot clinical studies and case series correlation between the assay’s results and clinically relevant parameters are lacking (Brandhorst, 2013; Liu, 2014).

Other cellular function assays

Cellular function assays (for example, the CU Index [CUI]) have also been investigated as a method to test for chronic urticaria. However, there is insufficient evidence in the published peer reviewed literature to support the use of cellular function assays for this use. Several recent studies (Chow, 2013; Lapolla, 2012) have reported that a positive CUI may not correlate with disease severity and a positive CUI is not present in all those with chronic urticaria.

In 2014, the American Academy of Allergy, Asthma and Immunology (AAAAI) the American College of Allergy Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma & Immunology jointly published an update to the practice parameter, *The Diagnosis and Management of Acute and Chronic Urticaria*, in which the following conclusion was made:

> Although commercial assays are now available, the utility of testing for autoantibodies to the high-affinity IgE receptor or autoantibodies to IgE has not been established. Whether detection of autoantibodies identifies a clinically unique population or will lead to a change in management is also currently unclear. Although some studies have suggested that a positive autoantibody test result might indicate a marker of increased disease severity, data are limited and might reflect the fact that these populations do not differ clinically and that these autoantibodies might represent an epiphenomenon.

The iSpot Lyme™ test is a variation of an enzyme-linked immunospot assay (ELISPOT) used to diagnose, confirm and monitor treatment response to Lyme disease. The iSpot is a T cell-based assay that identifies and measures the immune mediated T cell response to borrelia burgdorferi, the bacterium that causes Lyme disease.

In a 2014 prospective study, Nordberg and colleagues evaluated the performance of ELISPOT in the diagnosis of a disseminated form of Lyme borreliosis which affects the nervous system called Lyme neuroborreliosis (LNB). In this variation of Lyme disease, cerebrospinal fluid (CSF), rather than blood, is used to confirm the diagnosis. The study included 14 individuals with LNB and 103 individuals with non-LNB. ELISPOT analysis was used to assess for spontaneous and Borrelia-induced IFN-gamma secreting cells in the CSF. The ELISPOT results did not support that the ELISPOT is a useful supplementary diagnostic tool, showing only a sensitivity of 36% and a specificity of 82%.

In a study by Jin and associates (2013), blood samples of 25 individuals with Lyme disease were compared against the blood samples of 80 individuals with non-Lyme disease. The non-Lyme group included individuals with other clinical complications such as fibromyalgia, mononucleosis, rheumatoid arthritis and chronic fatigue syndrome. All blood samples were processed under two different methods, using the iSpot technique as well as the Western blot technique. The iSpot Lyme assay significantly increased the Borrelia-specific T cells' detection sensitivity ($p=0.001$) without increasing the false positive rate among the control group. The authors then compared peripheral blood samples from 80 healthy individuals not exposed to Borrelia, 25 individuals with clinically diagnosed Lyme disease, and 23 without Lyme disease but with clinically similar symptoms. The iSpot assay differentiated between non-Lyme disease participants and Lyme disease participants with a significance level of $p<0.0001$. The authors noted that compared to conventional ELISPOT, the iSpot had sensitivity of 84% versus 67%, a specificity of 94% versus 76%, a positive predictive value (PPV) of 81% versus 48%, and a negative predictive value (NPV) of 95% versus 86%, respectively. In those individuals with Lyme disease included in the study, the western blot showed 30% positivity while the iSpot and conventional ELISPOT assay showed an 84% and 50% positivity, respectively. In comparison, for the individuals without Lyme disease, the Western blot showed a 36% false positive rate while the conventional ELISPOT and iSpot did not report any cases. Although the results of this study appear promising, there are several limitations associated with it. This is the only published study of the iSpot Lyme test and it was sponsored and conducted by the iSpot manufacturer which introduces the potential for bias; there have been no studies completed by independent laboratories. In addition, the iSpot was not compared to the currently accepted "gold standard" for Lyme disease diagnosis. At this time, it appears the iSpot Lyme has been removed from the market

Background/Overview

The immune cell function assays have been proposed to assess the immune function of the transplant recipient in order to individualize therapy. They have also been investigated as a method of identifying those at risk for early acute kidney transplant rejection prior to the actual kidney transplant and for the management of a variety of other conditions such as autologous and allogeneic hematopoietic stem-cell transplant recipients, Lyme disease, immunodeficiency diseases including SCID and HIV, and immune mediated disorders including multiple sclerosis, and RA.

When organ rejection is suspected, a biopsy of the transplanted organ can confirm rejection. A routine biopsy is also often performed to detect rejection early, before symptoms develop. Additional tests may be performed prior to organ biopsy dependent on the type of transplant, and may include:

- Abdominal CT scan
- Bronchoscopy
- Chest x-ray
- Heart echocardiography
- Kidney arteriography
- Kidney ultrasound
- Lab tests of kidney or liver function

Lyme disease is typically diagnosed in two different ways. The presence or reported recent presence of an erythema migrans lesion, along with a compatible epidemiologic and clinical history, is sufficient for the diagnosis of Lyme disease. In fact, in this early, localized phase when an erythema migrans lesion may be present, serologic testing has been shown to be insensitive. Due to the nonspecificity of symptoms which can be associated with Lyme disease, the manifestation of an erythema migrans lesion is the only clinical symptom for which serologic confirmation is not required. In those cases in which there is diagnostic uncertainty, the Centers for Disease Control (CDC) recommends a two-tier testing approach (CDC, 2021). An initial enzyme immunoassay (EIA), followed by confirmation of all indeterminate or positive EIA tests with an immunoblot is currently recommended. Laboratory testing results are only considered positive when both tests are positive

The ImmuKnow assay received FDA clearance through the 510(k) process in 2002 for the detection of CMI response in populations undergoing immunosuppressive therapy for organ transplant. Pleximmune is an FDA-approved blood test to predict the risk of acute cellular rejection after a liver or intestine transplant in children and Pleximark is a blood test to assess the likelihood of rejection after a kidney transplant. Evidence is insufficient at this time to establish whether or not immune cell function assays are as beneficial as the established alternatives or result in improved clinical outcomes for any indication.

Definitions

Allogeneic stem cells: Stem cells harvested from a donor.

Autologous stem cells: Stem cells harvested from the individual's own bone marrow prior to the cytotoxic therapy.

Cell mediated immunity: An immune response caused by killer cells, not antibodies.

Cytotoxic: Destructive to cells.

Graft versus host disease: A life-threatening complication of bone marrow transplant in which the donated marrow causes an immune reaction against the recipient's body.

Phytohemagglutinin (PHA): Lectins (extract of kidney beans) capable of causing erythrocytes and leukocytes to clump together; a global stimulator of the immune system.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

81560	Transplantation medicine (allograft rejection, pediatric liver and small bowel), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score Pleximmune™, Plexision, Inc
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as an immune cell function assay]
86352	Cellular function assay involving stimulation (eg, mitogen or antigen) and detection of biomarker (eg, ATP)
0018M	Transplantation medicine (allograft rejection, renal), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score Pleximark™, Plexision, Inc

ICD-10 Diagnosis

	All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale, References and Websites sections.
Reviewed	11/10/2022	MPTAC review. Updated Description/Scope, Rationale, Background/Overview, References and Websites sections.
Reviewed	11/11/2021	MPTAC review. Updated Description/Scope, Background/Overview, References and Websites sections. Updated Coding section with 01/01/2022 CPT changes to add 81560; also added CPT codes 0018M and 81599.
Reviewed	11/05/2020	MPTAC review. Updated References and Websites sections.
Reviewed	11/07/2019	MPTAC review. Updated Background/Overview, References and Websites sections.
Revised	01/24/2019	MPTAC review. Removed iSpot from NMN criteria. Updated Description/Scope, NMN Statement, Rationale Background/Overview, and References sections.
Reviewed	02/27/2018	MPTAC review. Updated header language from “Current Effective Date” to “Publish Date.” Updated References section.
Reviewed	02/02/2017	MPTAC review. Updated Description/Scope, Rationale, and References sections.
Revised	02/04/2016	MPTAC review. Added iSpot for Lyme disease testing to Investigational and Not Medically Necessary Statement. Updated Rationale, Background/Overview and Reference sections. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review. Rationale and Reference sections updated
Reviewed	05/15/2014	MPTAC review. Rationale and Reference sections updated.
Revised	05/09/2013	MPTAC review. Position statement updated with the addition of urticaria. Rationale and Reference sections updated.
Revised	05/10/2012	MPTAC review. Description, Rationale, and Reference sections updated. Note added in Description section stating: “This document does not address laboratory testing for urticaria.” Rheumatoid arthritis added to the investigational and not medically necessary statement. Separated out immunodeficiency diseases from immune mediated disorders in the investigational and not medically necessary statement. Minor wording updates made in the investigational and not medically necessary statement including deletion of the word “for” at the beginning of each bullet point.
Revised	05/19/2011	MPTAC review. Investigational and not medically necessary position statement updated to include “all indications” and a list of possible indications added. Title, Description, Rationale, Discussion, and Reference sections updated.
Reviewed	05/13/2010	MPTAC review. Rationale, background and references updated.
	01/01/2010	Updated Coding section with 01/01/2010 CPT changes.
Reviewed	05/21/2009	MPTAC review. Rationale, background and references updated.
New	05/15/2008	MPTAC review. Initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.