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Corporate Medical Policy

Immune Cell Function Assay for Organ Transplant Rejection AHS-G2098

File Name: immune_cell_function_assay_for_organ_transplant_rejection
Origination: 1/1/2019
Last CAP Review: 3/2021
Next CAP Review 3/2022
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Description of Procedure or Service

Immune cell function assays involve measurement of peripheral blood lymphocyte response (intracellular ATP levels, proliferation) following stimulation to assess the degree of functionality of the cell-mediated immune response (Buttgereit, Burmester, & Brand, 2000).

Related Policies:
Flow Cytometry AHS-F2019
Transplant Rejection Testing AHS-M2091

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Reimbursement is not allowed for an immune cell function assay for organ transplant rejection for all applications.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Immune Cell Function Assay for Organ Transplant Rejection is covered

Not applicable

When Immune Cell Function Assay for Organ Transplant Rejection is not covered

Reimbursement is not allowed for an immune cell function assay for all indications including, but not limited to:

a) Management of solid organ transplant rejection in an individual undergoing immunosuppressive therapy;

b) Identification of risk for rejection prior to any solid organ transplantation;

c) Management of autologous or allogeneic hematopoietic stem cell transplantation;

d) Management of immunodeficiency disorders including human immunodeficiency virus (HIV) and severe combined immunodeficiency disease (SCID);

e) Management of or prediction of infection risk in immune mediated disorders including rheumatoid arthritis (RA), multiple sclerosis, and lupus nephritis;

f) Testing for urticaria;

g) Diagnosis and management of Lyme disease (for example, iSpot Lyme Test).

h) Management of inflammatory bowel diseases;

i) Monitoring immune response following surgery.

Policy Guidelines

Primary immunodeficiencies occur in as many as 1:2000 live births. They are most often categorized according to a combination of mechanistic and clinical descriptive characteristics (Bonilla et al., 2015).

Specific cellular immunity is mediated by T cells, and defects affecting these T cells underlie the most severe immunodeficiencies. As antibody production by B cells requires intact T cell function, most T cell defects lead to combined (cellular and humoral) immunodeficiency (Bonilla & Stiehm, 2017).

In vitro studies of T cell function measure peripheral blood T cell response to several different types of stimuli (Bonilla, 2008):

- Mitogens (such as the plant lectins phytohemagglutinin, concanavalin A, pokeweed mitogen, anti-CD3).
- Specific antigens (such as tetanus and diphtheria toxoids or Candida albicans antigens).
- Allogeneic lymphocytes (ie, mixed lymphocyte culture).

Exposure of T cells to stimulus leads to their metabolic activation and polyclonal expansion (Fernandez-Ruiz, Kumar, & Humar, 2014).

Response can be measured by indicators of proliferation, ATP synthesis and release, or expansion of specific subpopulations (Bonilla & Stiehm, 2017).

Evaluation of specific immune responses is essential for diagnosis of primary immune deficiencies. Screening tests used to evaluate patients with suspected primary immune deficiencies are relatively inexpensive, performed rapidly, and reasonably sensitive and specific (Notarangelo, 2010; Oliveira & Fleisher, 2010). Abnormal screening test results indicate the need for more sophisticated tests. This stepwise approach ensures efficient and thorough evaluation of mechanisms of immune dysfunction that underlie the clinical presentation, with narrowing of diagnostic options before using costly sophisticated tests that might be required to arrive at specific diagnoses (Bonilla et al., 2015). Abnormal T cell counts T cell mitogen responses that are absent or extremely low, are a crucial element in the diagnosis of several primary immune deficiencies, most notably, SCID (Picard et al., 2015).

Additionally, T-cell recognition of alloantigen is the primary and central event that leads to the cascade of events that result in rejection of a transplanted organ (Vella, 2017). Several commercial assays have been developed based on the traditional assessment of T-cell stimulation to predict or assess transplant rejection.

The Immunoknow assay measures the ability of CD4 T-cells to respond to mitogenic stimulation by phytohemagglutinin-L in vitro by quantifying the amount of adenosine triphosphate (ATP) produced and released from these cells following stimulation. Since the CD4 lymphocytes orchestrate cell-mediated immunity responses through immunoregulatory signaling, measurement of intracellular ATP levels following CD4 activation is intended to estimate the net state of immune system in immunocompromised patients (Chon & Brennan, 2017) and one of the few well-established strategies for functional immune monitoring in solid organ transplant recipients (Sottong, Rosebrock, Britz, & Kramer, 2000).

Clinical Validity and Utility

A population-based study comparing the assay results in healthy controls and solid organ transplant recipients established three categories to define patient's cell-mediated immune response: strong ($\geqslant$525 ng ml^{-1}), moderate (226–524 ng ml^{-1}) and low ($\leqslant$225 ng ml^{-1}) (Fernandez-Ruiz et al., 2014; Kowalski et al., 2006).

Numerous authors have analyzed the predictive value of the Immunoknow assay for acute rejection, as recently summarized in a meta-analysis that found a relatively high specificity (0.75) but a low sensitivity (0.43), with significant heterogeneity across studies (Fernandez-Ruiz et al., 2014; Ling et al., 2012).

The ImmuKnow® (Cylex) assay has been examined in clinical trials for its potential use in monitoring immunosuppression medication regimens in solid organ transplant patients.

Chon and Brennan (2017) published a review on diagnostic methods for acute renal allograft rejection. Regarding the use of the Immuknow assay in acute renal allograft rejection, the authors stated that "At the present time, there is no consensus on the utility of these tests, other than in the research setting. Nonetheless, these assays may prove helpful both for diagnostic purposes and for monitoring the response to antirejection therapy."

Kowalski et al (2006) performed "a meta-analysis of 504 solid organ transplant recipients (heart, kidney, kidney-pancreas, liver and small bowel) from 10 U.S. centers was performed using the Cylex ImmuKnow assay." Which found that: "A recipient with an immune response value of 25 ng/ml adenosine triphosphate (ATP) was 12 times (95% confidence of 4 to 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% confidence of 8 to 112) more likely to develop a cellular rejection than a recipient with a lower immune response value. Of note is the intersection of odds ratio curves for infection and rejection in the moderate immune response zone (280 ng/ml ATP). This intersection of risk curves provides an immunological target of immune function for solid organ recipients." They concluded that "These data show that the Cylex ImmuKnow assay has a high negative predictive value and provides a target immunological response zone for minimizing risk and managing patients to stability."

Uemura et al. (2011) states, "immunosuppression management in post-transplant malignancy is challenging because of a lack of objective immunologic assessment tools." Therapeutic drug monitoring of immunosuppressants has been a key component in immunologic monitoring, but it has limitations. "Immunosuppressant drug monitoring has traditionally been the mainstay of immunologic monitoring, in conjunction with the patient's clinical status and graft function, but it does not take into account the high degree of patient variation in the metabolism of the immunosuppressant medication nor does it accurately reflect the synergistic effect of combination immunosuppressant therapy. Pharmacokinetic monitoring has been recognized as being more effective in preventing drug toxicity and as being less effective in predicting functional efficacy. Thus, single trough levels of immunosuppressive agents do not reflect the overall degree of immunosuppression in a patient" (Uemura, 2011).

Wang et al (2014) performed a meta-analysis of six studies which found "The pooled sensitivity, specificity, PLR, NLR, and DOR of ImmuKnow for predicting the risk of infection were 0.51 (95% confidence interval [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 DOR 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 PLR of 4.45 (95% CI, 0.91-21.74), and an NLR of 0.35 (95% CI, 0.08-1.45), was found in the analysis of the predictive value for acute rejection. The summary receiver operating characteristic curve values for ImmuKnow in distinguishing patients with infections from those with acute rejections were 0.631 ± 0.215 and 0.986 ± 0.015, respectively." They 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."

Jo et al (2015) "analyzed CD4 T-lymphocytes ATP levels along with lymphocyte subsets in 160 samples from 111 post-allogeneic hematopoietic stem cell transplantation (alloHSCT) patients. In patients with stable status, ImmuKnow levels changed over time and the 6-month post-alloHSCT levels were significantly higher than those tested within 6 months post-alloHSCT ($P < 0.001$). Although, ImmuKnow levels for acute graft-versus-host disease (GVHD) or infection episodes were not significantly different compared to those for stable alloHSCT, the levels were correlated with specific

lymphocyte subpopulations at different times; the results within 6 months post-alloHSCT showed low positive correlation with natural killer cell count ($r = 0.328$) ($P < 0.05$) and the values tested later than 6 months post-alloHSCT were positively correlated with CD4 T cell count ($r = 0.425$) ($P < 0.05$). Two patients who developed acute GVHD and two who experienced an infection episode showed increased ImmuKnow levels in sequential tests. The combined test of ImmuKnow levels and lymphocyte subsets may be helpful for immune monitoring following alloHSCT."

Ravaioli et al (2015) aimed to "assess the clinical benefits of adjusting immunosuppressive therapy in liver recipients based on immune function assay results" in which "Adult liver recipients were randomized to standard practice (control group; n = 102) or serial immune function testing (interventional group; n = 100)". "Based on immune function values, tacrolimus doses were reduced 25% when values were less than 130 ng/mL adenosine triphosphate (low immune cell response) and increased 25% when values were greater than 450 ng/mL adenosine triphosphate (strong immune cell response)." They found that: "The 1-year patient survival was significantly higher in the interventional arm (95% vs 82%; $P < 0.01$) and the incidence of infections longer than 14 days after transplantation was significantly lower among patients in the interventional arm (42.0% vs. 54.9%, $P < 0.05$). The difference in infection rates was because of lower bacterial (32% vs 46%; $P < 0.05$) and fungal infection (2% vs 11%; $P < 0.05$). Among recipients without adverse events, the study group had lower tacrolimus dosages and blood levels." They concluded "Immune function testing provided additional data which helped optimize immunosuppression and improve patient outcomes."

Piloni et al (Piloni et al., 2016) "measured functional immunity in lung transplant recipients and correlated Immuknow values with immunosuppression levels, presence of chronic lung allograft dysfunction (CLAD) and infections. We evaluated 61 lung recipients who underwent follow-up for lung transplantation between 2010 and 2014. Rejection and infection were retrospectively analyzed. The association between over-immunosuppression and a number of predictors was assessed by means of univariate and multivariate logistic regression models. 71 out of 127 samples (56%) showed an over-immunosuppression with an ImmuKnow assay mean level of 112.92ng/ml (SD±58.2), vs. 406.14ng/ml (SD±167.7) of the rest of our cohort. In the over-immunosuppression group we found 51 episodes of infection (71%) (OR 2.754, 95% CI 1.40-5.39; P-value 0.003). In the other group, only 25 samples (44%) were taken during an infectious episode. The mean absolute ATP level was significantly different between patients with or without infection (202.38±139.06ng/ml vs. 315.51±221.60ng/ml; $P<0.001$). RAS (Restrictive allograft syndrome) was associated to low ImmuKnow level ($P<0.001$). These results were confirmed by the multivariate analysis. The ImmuKnow assay levels were significantly lower in infected lung transplant recipients compared with non-infected recipients and in RAS patients."

Chiereghin et al (2017) "retrospectively reviewed the symptomatic infectious episodes that occurred during the first-year post-transplant to determine time of onset, causative pathogens and cell-mediated immunity response patterns. Ninety-eight of the 202 (48.5%) recipients enrolled developed at least one infectious episode. The total number of infectious episodes was 135: 77 (57.1%) bacterial, 45 (33.3%) viral and 13 (9.6%) fungal. The most frequently isolated bacteria were Escherichia coli (21 isolates) and Klebsiella pneumoniae (19 isolates). Overall, extended-spectrum beta lactamase-producing and methicillin-resistant organisms were responsible for 29 (29/77; 37.7%) infectious episodes. Members of the herpes virus group, in particular cytomegalovirus (34/45 viral infections, 75.5%), were detected. Candida species (9 isolates) followed by Aspergillus species (4 isolates) were isolated. The majority of infections (63%) occurred during the early post-transplant phase (<1 month), whereas only 8/135 episodes (5.9%) were detected after the sixth month (late phase). Significantly lower median ImmuKnow® intracellular ATP values in patients who developed bacterial and fungal infections compared to infection-free patients were observed ($P < 0.0001$ and $P = 0.0016$, respectively), whereas patients who developed a viral infection had a median intracellular ATP level not statistically different compared to uninfected patients ($P = 0.4$). Our findings confirm that bacteria are responsible for the majority of symptomatic infections and occur more frequently during the first month post-transplant. The ImmuKnow® measurements can be a useful tool for identifying patients at high risk of developing infection, particularly of fungal and bacterial etiology."

However, At the present time, there is no consensus on the utility of these tests, despite the amount of literature devoted to determine its real value for predicting post-transplant complications (Fernandez-Ruiz et al., 2014; Kowalski et al., 2006; Ling et al., 2012; Rodrigo et al., 2012).

The Pleximmune™ blood test measures the inflammatory immune response of recipient T-cells to the donor in co-culture of lymphocytes from both sources (Ashokkumar et al., 2009; Ashokkumar et al., 2017; Sindhi et al., 2016). Pleximmune test sensitivity and specificity for predicting acute cellular rejection is 84% and 81% respectively in training set–validation set testing of 214 children. Early clinical experience shows that test predictions are particularly useful in planning immunosuppression in the setting of indeterminate biopsy findings, or in modifying protocol-mandated treatment when combined with all other available clinical information about an individual patient (Sindhi et al., 2016).

Pleximmune has recently been developed and only data from it approval has been published. Ashokkumar et all (2017) published a study designed "To establish safety and probable benefit, CD154+TcM were measured in cryopreserved samples from 214 children younger than 21 years (National Clinical Trial 1163578). Training set samples (n = 158) were tested with research-grade reagents and 122 independent validation set samples were tested with current good manufacturing practices-manufactured reagents after assay standardization and reproducibility testing. Recipient CD154+TcM induced by stimulation with donor cells were expressed as a fraction of those induced by HLA nonidentical cells in parallel cultures. The resulting immunoreactivity index (IR) if greater than 1 implies increased rejection-risk." The authors found that "Training and validation set subjects were demographically similar. Mean coefficient of test variation was less than 10% under several conditions. Logistic regression incorporating several confounding variables identified separate pretransplant and posttransplant IR thresholds for prediction of rejection in the respective training set samples. An IR of 1.1 or greater in posttransplant training samples and IR of 1.23 or greater in pretransplant training samples predicted LTx or ITx rejection in corresponding validation set samples in the 60-day postsampling period with sensitivity, specificity, positive, and negative predictive values of 84%, 80%, 64%, and 92%, respectively (area under the receiver operator characteristic curve, 0.792), and 57%, 89%, 78%, and 74%, respectively (area under the receiver operator characteristic curve, 0.848). No adverse events were encountered due to phlebotomy." They concluded that "Allospecific CD154+T-cytotoxic memory cells predict acute cellular rejection after LTx or ITx in children. Adjunctive use can enhance clinical outcomes."

State and Federal Regulations, as applicable

ImmuKnow® (Viracor, previously, Cylex) is an immune cell function assay cleared for marketing by the U.S. Food and Drug Administration (FDA) in April 2002 to detect cell-mediated immunity (CMI) in an immunosuppressed patient population. Cylex obtained 510(k) clearances from the FDA to market the Immune Cell Function Assay based on substantial equivalence to two flow cytometry reagents. The FDA-indicated use of the Cylex Immune Cell Function Assay is for the detection of cell-mediated immunity in an immunosuppressed population. A subsequent 510(k) marketing clearance for a device modification was issued by the FDA for this assay in 2010. 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.

Practice Guidelines and Position Statements

The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI)

The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) published practice parameters for the diagnosis and management of primary immunodeficiency (Bonilla et al., 2015) which stated that:

"Evaluation of specific immune responses is essential for diagnosis of PIDDs. Measurement of serum immunoglobulin levels and lymphocyte responses to mitogens are useful indicators of global B- and T-cell development and function."

It lists “In vitro proliferative response to mitogens and antigens” as an advanced test used when “Abnormal screening test results indicate the need for more sophisticated tests”. The screening test indicated is: Flow cytometry to enumerate CD4 and CD8 T cells and NK cells.

Normal or abnormal T cell response to mitogen stimulation is listed in the diagnostic algorithm for the diagnosis of combined or syndromic immunodeficiencies. Specifically, it states that “Infants with low TREC counts should have secondary screening by using flow cytometry to enumerate T-cell numbers and the proportion of naive cells. T-cell counts of less than 1500/mm3 or a proportion of naive cells of less than 50% should be followed up measuring the in vitro response to a mitogen, such as PHA. It is also listed as a characteristic laboratory finding for WAS, AT related disorders, Good syndrome, XLP1, MSMD, MyD88, WHIM, EV and in the management of DGS, and immuno-osseous dysplasias.

The 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®. Educational guidelines for the management of kidney transplant recipients in the community setting and for infectious diseases in transplant recipients published in 2009 by the American Society of Transplantation (AST) do not include ImmuKnow®.

The American Society of Transplantation

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 Cytomegalovirus CMV Consensus Group of the 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 (Kotton et al). 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 86352

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 11/2019

Specialty Matched Consultant Advisory Panel 3/2020

Medical Director review 3/2020

Medical Director review 10/2020

Specialty Matched Consultant Advisory Panel 3/2021

Medical Director review 3/2021

Policy Implementation/Update Information

1/1/2019 New policy developed. Immune cell function assay for organ transplant rejection is considered investigational for all applications. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

10/1/2019 Policy Statement revised to read: Reimbursement is not allowed for an immune cell function assay for organ transplant rejection for all applications. Wording revised in the Not Covered

section. “Investigational” changed to read “Reimbursement is not allowed…” Deleted coding grid. Notification given 10/1/2019 for effective date 12/2/2019. (an)

12/10/19 Reviewed by Avalon 3rd Quarter 2019 CAB. No change to policy statement. Medical Director review 11/2019. (lpr)

3/31/20 Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (lpr)

11/10/20 Reviewed by Avalon 3rd Quarter 2020 CAB. Literature review only. Updated references and added Related Policy section. Medical Director review 10/2020. (lpr)

4/6/21 Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr)