FirstChoice VIP CARE
by Select Health of South Carolina

Immune cell function assay

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

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Coverage policy

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

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Standard of care patient evaluation and management by a network transplantation health care provider.

Background

Cellular immune function is an important factor in risk for acute graft rejection, opportunistic infection, and cancer among immunosuppressed transplant recipients (Bestard, 2017). Immune status monitoring is necessary to balance the risk of immunosuppressant therapy and drug-related toxicity. The most frequently used tools to monitor immunosuppression in transplant recipients are therapeutic drug levels in the blood, antihuman leukocyte antigen antibody assays, and the presence of opportunistic infections, but they are often insufficient to differentiate rejection from toxicity, necessitating allograph biopsy.

Immune cell function assays are biomarkers that quantify T-cell and B-cell alloreactivity noninvasively, some of which may also provide important information in the management of autoimmune diseases (Bestard, 2017). These tests may address an unmet need for a safer, more tolerable, and cost-effective approach to immunosuppression.

Pleximmune:
Pleximmune is a qualitative prognostic test that measures the inflammatory response of T-cytotoxic memory lymphocytes to donor cells and reports the results as a numeric score called the immunoreactivity index (Plexision, 2020). The index is compared with a rejection-risk threshold developed from testing of over 200 liver or intestine recipients to assign risk. The U.S. Food and Drug Administration (2014) approved Pleximmune under a Humanitarian Device Exemption for prediction of acute cellular rejection within 60 days after transplantation in patients less than 21 years old with liver or small bowel transplantation. It is intended to be used in the pre-, early-, and late-transplantation periods in conjunction with biopsy, standard clinical assessment, and other laboratory information (U.S. Food and Drug administration, 2019).

ImmuKnow:
ImmuKnow measures the adenosine triphosphate response of stimulated peripheral blood lymphocytes (CD4+ T-cells) as an index of lymphocyte activity. The measurement of CD4 activation reflects the degree of immune function (Eurofins Viracor, 2020). The U.S. Food and Drug Administration (2002) issued 510(k) approval for detection of cell-mediated immunity in solid organ transplant recipients receiving immunosuppressive therapy (Huskey, 2011).

Findings

The American Society of Transplantation does not mention the use of the ImmuKnow immune cell function assay in its recommendations for the screening, monitoring, and reporting of infections and complications in the evaluation of recipients of organ transplantation (Humar, 2006, reaffirmed 2013). An article representing the Society's position notes the large variability in sensitivity (ability to detect early viral infection) in transplant patients); the 11 types of assays listed do not include immune cell function assay (Fishman, 2009).

A meta-analysis (Wang, 2014) of six studies determined that, for predicting infection, ImmuKnow had a sensitivity of 0.51, specificity of 0.75, a positive likelihood ratio of 1.97, a negative likelihood ratio of 0.67, and a diagnostic odds ratio of 3.56. For predicting acute rejection, the results were sensitivity of 0.51, specificity of 0.90, a positive likelihood ratio of 4.45, a negative likelihood ratio of 0.35, and a diagnostic odds ratio of 13.81) The authorsconcluded that the data did not support the use of the ImmuKnow assay to predict or monitor the risks of infection and acute rejection in renal transplant recipients.

A meta-analysis (Rodrigo, 2012) assessed ImmuKnow as a diagnostic tool for predicting infection (five studies) and acute rejection (five studies) in adults after liver transplantation. For predicting infection, ImmuKnow demonstrated a sensitivity of 0.84 and a specificity of 0.75. According to the diagnostic odds ratio, transplant recipients with a positive ImmuKnow result had 14.6 greater odds of having an infection than patients with a negative test result, and a positive likelihood ratio of 3.3 suggests that a positive ImmuKnow result increases the post-test probability of infection. In contrast, ImmuKnow's test performance for acute rejection could not be validated due to considerable heterogeneity across studies.

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

estimates for identifying risk of rejection were also fairly poor with a sensitivity of 0.43, a specificity of 0.75, a positive likelihood ratio of 1.30, a negative likelihood ratio of 0.96, and a diagnostic odds ratio of 1.19.

A meta-analysis of 504 solid organ transplant recipients tested with ImmuKnow found 39 biopsy rejections and 66 infections. Recipients with an immune response value of 25 ng/ml adenosine triphosphate had 12 times the risk of infection than those with a stronger immune response. Recipients with a value of 700 ng/ml had 30 times the risk of cellular rejection than those with a lower immune response (Kowalski, 2006).

A study of 864 ImmuKnow assays performed on 296 heart transplant patients up to 10 years after transplant detected 38 infectious episodes, during which the average immune monitoring score was significantly lower during infection than steady state (187 versus 280 ng ATP/ml, $P < .001$). The article reported finding only eight rejection episodes (Kobashigawa, 2010).

A study of 1330 ImmuKnow assays in 583 renal transplant recipients analyzed values to episodes of infection or rejection within 90 days of transplant, versus controls (transplant patients matched for age, gender, and time of testing without clinical events). No difference existed between group in patients with infections (n = 94, 386 versus 417 ng/ml, $P = .24$), or in patients with rejection (n = 47, 390 versus 432 ng/ml, $P = .25$), and authors conclude that ImmuKnow does not aid in predicting infection or rejection (Huskey, 2011).

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

An analysis of 897 T-cell assay (ImmuKnow) results in 414 renal transplant patients showed nearly 40% of patients experienced a decrease of >150 ng/mL from 1 – 6 months after the procedure ($P < .0001$). The decrease flattened in the period 6 – 12 months after ($P = .33$). T-cell assay ≤ 225 ng/mL was associated with BK virus infection only at 12 months ($P = .005$), suggesting that patients with low values after six months may benefit from tailoring of immunosuppression or more monitoring to prevent infection (Gralla, 2012).

An article on 248 recipients of liver transplants showed the average ImmuKnow adenosine triphosphate value in the 109 patients who developed invasive fungal infections was significantly lower than that in those with common bacterial infections ($P < .01$) or stable liver recipients ($P < .01$). Thus, ImmuKnow assays may identify patients at risk of developing such infections after liver transplantation (Zhou, 2012).

A study of 4,224 assay values in 306 renal transplantation patients showed that average ImmuKnow assay levels after transplant were 461 (0-1 week), 519 (1 week-1 month), 411 (1-3 months), 344 (3-12 months), and 405 (thereafter). This trend was similar to that of peripheral white blood cell counts ($P < .0001$), but did not correspond with risk of infection/rejection. ImmuKnow assay results should be interpreted cautiously (Sageshima, 2014).

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

A randomized controlled study of 202 solid organ transplant recipients included those with serial immune function testing after surgery using ImmuKnow and controls/standard practice. Tacrolimus doses were reduced 25% (< 130 ng/mL adenosine triphosphate, or low immune cell response) and increased 25% (> 450 ng/mL adenosine

triphosphate, or strong immune cell response). The ImmuKnow group had longer one-year survival (95% versus 82%; *P* < .01) and fewer infections > 14 days after transplant (42.0% vs. 54.9%, *P* <.05) (Ravaioli, 2015).

One study evaluated the diagnostic accuracy of the Pleximmune test (Sindhi, 2016). The sensitivity and specificity of Pleximmune for predicting acute cellular rejection were 0.84 and 0.80, respectively, in training set-validation set testing of 214 children (Ashokkumar, 2017; Sindhi, 2016).
A review of $CD4^+$ T-cell intracellular adenosine triphosphate levels analyzed by ImmuKnow assay in 273 liver transplantation patients concluded survival is correlated with these levels, the peak occurring in the first three months following the procedure (Qu, 2017).

A study of 705 pediatric patients undergoing liver transplantation detected Epstein-Barr Virus infection in 468 (66.4%). ImmuKnow assay testing documented overall immune response was significantly lower than in non-infected patients (*P* < .0001), supporting authors' conclusion that ImmuKnow may provide guidance in reducing immunosuppressive agents in treating post-transplant lymphoproliferative disorder (Qin, 2020).

From June 1, 2018 to May 31, 2019: 576 Pleximmune tests were performed on 396 patients without any new or unexpected risks for the pediatric patients as compared with the premarket analysis therefore the U.S. Food and Drug Administration (2020) concluded that it is a useful adjunct and the probable benefit to health outweighs the risks but surveillance will be continued.

The use of immune functional assays prove to be invaluable in the revealing precious information, anticipating response to therapy and fight against pathogen, and improving patient outcomes as compared to using circulating and cell surface biomarker measurements after in vitro exposure. Latent tuberculosis infection is an example of how T-cell mediated immunity assays, revolutionized detection of this disease, which have been developed more recently. Although encouraging results, the main challenge remains due to a need for standardization methods employed in clinical settings to use immune function assays and obtain reliable reproducible results. Another pitfall is the individualized variability of the immune response (Mouton, 2020).

References

On January 3, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "ImmuKnow," "immune cell function assay," and "Pleximmune." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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