

Protocol

Immune Cell Function Assay

(20456)

Medical Benefit		Effective Date: 04/01/12	Next Review Date: 01/20
Preauthorization	No	Review Dates: 09/10, 09/11, 01/12, 01/13, 01/14, 01/15, 01/16, 01/17, 01/18, 01/19	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With a solid organ transplant	Interventions of interest are: • Immune cell function assay with ImmuKnow	Comparators of interest are: • Standard monitoring of immunosuppression	Relevant outcomes include: • Overall survival • Test accuracy • Other test performance measures • Morbid events
Individuals: • With a hematopoietic cell transplant	Interventions of interest are: • Immune cell function assay with ImmuKnow	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Test accuracy • Other test performance measures • Morbid events
Individuals: • With a solid organ transplant	Interventions of interest are: • Immune cell function assay with Pleximmune	Comparators of interest are: • Standard monitoring of immunosuppression	Relevant outcomes include: • Overall survival • Test accuracy • Other test performance measures • Morbid events
Individuals: • With a hematopoietic cell transplant	Interventions of interest are: • Immune cell function assay Pleximmune	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Test accuracy • Other test performance measures • Morbid events

DESCRIPTION

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

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 on 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.

POLICY

Use of the immune cell function assay to monitor and predict immune function after solid organ transplantation is considered **investigational**.

Use of the immune cell function assay to monitor and predict immune function after hematopoietic cell transplantation is considered **investigational**.

Use of the immune cell function assay for all other indications is considered **investigational**.

BACKGROUND

IMMUNOSUPPRESSION FOR TRANSPLANT

In current clinical practice, levels of immunosuppression in patients being managed after a solid organ transplant or hematopoietic cell transplantation are determined by testing for clinical toxicity (e.g., leukopenia, renal failure) and by therapeutic drug monitoring when available. However, drug levels are not a surrogate for overall drug distribution or efficacy because pharmacokinetics often differ among individuals due to clinical factors such as underlying diagnosis, age, sex, and race; circulating drug levels may not reflect the drug concentration in relevant tissues; and serum level of an individual immunosuppressant drug may not reflect the cumulative effect of other concomitant immunosuppressants. The main value of therapeutic drug monitoring is the avoidance of toxicity. Individual immune profiles, such as an immune cell function assay, could support clinical decision mak-

ing and help to manage the risk of infection from excessive immunosuppression and the risk of rejection from inadequate immunosuppression.

Treatment

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

ImmuKnow measures the concentration of adenosine triphosphate (ATP) in whole blood after a 15- to 18-hour incubation with phytohemagglutinin (a mitogenic stimulant). Cells that respond to stimulation show increased ATP synthesis during incubation. Concurrently, whole blood is incubated in the absence of stimulant for the purpose of assessing basal ATP activity. CD4-positive T lymphocytes are immunoselected from both samples using anti-CD4 monoclonal antibody-coated magnetic particles. After washing the selected CD4-positive cells on a magnet tray, a lysis reagent is added to release intracellular ATP. A luminescence reagent added to the released ATP produces light measured by a luminometer, which is proportional to the concentration of ATP. The characterization of the cellular immune response of a specimen is made by comparing the ATP concentration for that specimen with fixed ATP production ranges.

Pleximmune measures CD154 expression on T-cytotoxic memory cells in patient's peripheral blood lymphocytes. CD154 is a marker of inflammatory response. To characterize the 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 an increased risk of rejection, and an IR less than 1.1 indicates a decreased risk of rejection. For pretransplant samples, the threshold for IR is 1.23.

REGULATORY STATUS

In April 2002, ImmuKnow® (Cylex, acquired by ViraCor-IBT Laboratories, 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 the FDA through the 510(k) process. The FDA-indicated use of the Immune Cell Function Assay is for the detection of cell-mediated immune response in an immunosuppressed population. In 2010, a device modification for this assay was cleared for marketing by the FDA through the 510(k). There were no changes to the indications or intended use.¹

In August 2014, Pleximmune™ (Plexision, Pittsburgh, PA) was approved by the FDA through the humanitarian device exemption process.² The test is intended for use in the pretransplantation and early and late post-transplantation period in pediatric liver and small bowel transplant patients for the purpose of predicting the risk of transplant rejection within 60 days after transplantation or 60 days after sampling.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced

procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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