Immune Cell Function Assay

Description of Procedure or Service

Careful monitoring of lifelong immunosuppression is required to ensure long-term viability of solid organ allografts without incurring increased risk of infection. Monitoring of immunosuppression 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.

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 differs 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.

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 the mitogenic stimulant, phytohemagglutinin. 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 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 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
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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.

**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 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.

***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**

**Immune Cell Function Assay** is considered investigational for all applications. BCBSNC does not cover investigational services or procedures.

**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 is covered**

Not applicable.

**When Immune Cell Function Assay is not covered**

The immune cell function assay is considered investigational for all indications, including to monitor and predict immune function after solid organ transplantation or hematopoietic stem cell transplantation.

BCBSNC does not cover investigational services.

**Policy Guidelines**

For individuals who have a solid organ transplant or hematopoietic cell transplant (HCT) who receive testing with an immune cell function assay with ImmuKnow, the evidence includes numerous studies of the association of assay test values and subsequent rejection or infection, and 1 randomized controlled trial in liver transplant patients. Relevant outcomes are overall survival, test accuracy, other test performance measures, and morbid events (rejection and infection). The ImmuKnow test shows
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variable associations with infection and rejection depending on the type of transplant and the 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 HCT who receive testing using an immune cell
function assay with Pleximmune, the evidence includes Food and Drug Administration (FDA)
documentation and 1 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 FDA 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 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 so the clinical validity is uncertain. The
evidence is insufficient to determine the effects of the technology on health outcomes.

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

***Please note: 86352 is not specific to this policy and may be submitted for other laboratory tests.

Providers should not submit claims using CPT codes 86353 and/or 82397.

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

Immune Cell Function Assay in Solid Organ Transplantation

Humar A, Michaels M; AST ID Working Group on Infectious Disease Monitoring. American Society
of Transplantation recommendations for screening, monitoring and reporting of infectious
complications in immunosuppression trials in recipients of organ transplantation. Am J Transplant


Senior Medical Director - 10/2009
Senior Medical Director - 12/2009


An Independent Licensee of the Blue Cross and Blue Shield Association
Immune Cell Function Assay

**Policy Renamed - Immune Cell Function Assay**


**Policy Implementation/Update Information**

**Immune Cell Function Assay in Solid Organ Transplantation**

11/9/09 New Evidence Based Guideline issued. Reviewed with Senior Medical Director 10/16/2009.  
"Use of the immune cell function assay to monitor and predict immune function after solid organ transplantation is not recommended.” (bw)

1/5/10 Evidence Based Guideline converted to Corporate Medical Policy. "BCBSNC will not provide coverage for Immune Cell Function Assay in Solid Organ Transplantation because it is considered investigational. BCBSNC does not cover investigational services.” Added new CPT code, 86352, to the "Billing/Coding” section. Changed the wording of "Providers may be submitting claims using CPT codes 86353 and/or 82397." to "Providers should not be submitting claims using CPT codes 86353 and/or 82397." Notice given 1/5/2010. Policy effective 4/13/2010. (bw)

6/22/10 Policy Number(s) removed (amw)

7/6/10 Added statement to “Billing/Coding” section to indicate; "Please note: 86352 is not specific to this policy and may be submitted for other laboratory tests.” (bw)


**Policy Renamed - Immune Cell Function Assay**

4/17/12 Policy name changed from “Immune Cell Function Assay in Solid Organ Transplantation” to “Immune Cell Function Assay”. Additional investigational indications added; “The immune cell function assay is considered investigational for all indications, including to monitor and predict immune function after solid organ transplantation or hematopoietic stem cell transplantation. BCBSNC does not cover investigational services.” Notification given 4/17/12. Policy effective 7/24/12. Reference added. (bw)
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1/29/13 Description section revised. Policy Guidelines updated. Reference added. (btw)

4/16/13 Specialty Matched Consultant Advisory Panel review 3/20/2013. No change to policy statement. (btw)

1/28/14 Policy Guidelines section updated. Reference added. (btw)


4/28/15 Specialty Matched Consultant Advisory Panel review 3/25/2015. Reference added. No change to policy intent. (lpr)

4/29/16 Description and Policy Guidelines sections updated. Reference added. Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)

1/27/17 Description, Policy Guidelines and Regulatory status sections updated. Reference added. No change to policy intent. (lpr)

4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)

1/12/18 Reference added. No change to policy statement. (lpr)

4/13/18 Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.