

Policy: MP236

Section: Medical Benefit Policy

Subject: Immune Cell Function Assay for Transplant Rejection

I. Policy: Immune Cell Function Assay for Transplant Rejection

II. Purpose/Objective:

To provide a policy of coverage regarding Immune Cell Function Assay for Transplant Rejection

III. Responsibility:

- A. Medical Directors
- B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

- (i) The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
- (ii) The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.
- (iii) The service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age.

DESCRIPTION:

Immune cell function assay is intended for use in the detection of cell mediated immunity (CMI) in patients undergoing immunosuppressive therapy post solid organ treatment. The assay is proposed to measure immune suppression and identify patients at risk for infection or rejection. The assay has also been proposed as a means of detecting insured individuals who may be at risk for transplant rejection *prior* to kidney or other solid organ transplantation.

EXCLUSIONS: The Plan does **NOT** provide coverage for the use of immune cell function assay for the measurement of organ transplant rejection following solid organ transplant because it is considered **experimental, investigational or unproven**. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this treatment on health outcomes when compared to established treatments or technologies.

The Plan does **NOT** provide coverage for the use of immune cell function assay for the identification of insured individuals at risk for rejection prior to kidney or any other solid organ transplantation because it is considered **experimental, investigational or unproven**. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this treatment on health outcomes when compared to established treatments or technologies.

SEE ALSO: MP168 Non-invasive Testing for Organ Transplant Rejection

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in MP 15 - Experimental Investigational or Unproven Services or Treatment.

CODING ASSOCIATED WITH: Immune Cell Function Assay for Transplant Rejection

The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.

86352 Cellular function assay involving stimulation (eg, mitogen or antigen) and detection of biomarker (eg, ATP) **note: this code is not covered when used to identify Immuknow™ Pleximmune™, myTAIHEART or CU Index® testing. Pleximmune™, CU Index®**

Current Procedural Terminology (CPT®) © American Medical Association: Chicago, IL

Associated Key Words: Immune Cell Function Assay, Immuknow™, Pleximmune™, myTAIHEART, CU Index®

LINE OF BUSINESS:

Eligibility and contract specific benefits, limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy. For PA Medicaid Business segment, this policy applies as written.

REFERENCES:

Geisinger TAC Triage Committee. Immune Cell Function Assay August 2010.

Bhorade SM, Janata K, Vigneswaran WT, et al. Cylex ImmuKnow assay levels are lower in lung transplant recipients with infection. J Heart Lung Transplant. 2008;27(9):990-994.

Israeli M, Klein T, Sredni B, Avitzur Y, Mor E, Bar-Nathen N, Steinberg R, Dinari G & Shapiro R. ImmuKnow: A new parameter in Immune Monitoring of Pediatric Liver Transplantation Recipients. Liver Transplantation 2008; 14:893-898.

Rossano JW, Denfield SW, Kim JJ et al. Assessment of Cylex ImmuKnow Cell Function Assay in Pediatric Heart Transplantation Patients. J Heart & Lung Transplantation 2009;28(1).

Husain S, Raza K, Pilewski JM et al. Experience with Immune Monitoring in Lung Transplant Recipients: Correlation of Low Immune Function with Infection. Transplantation 2009; 87:1852-1857.

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*. 2006; 6(2):262-274. Available at: http://www.a-s-t.org/files/pdf/knowledge_center/guidelines/ast_monitoring_guidelines.pdf. Accessed August 5, 2010.

U.S. Food and Drug Administration (FDA). Cylex Immune Cell Function Assay. 510(k) Summary. K013169. Rockville, MD: FDA; April 2, 2002. Available at: <http://www.fda.gov/cdrh/pdf/k013169.pdf>. Accessed August 5, 2010

Cylex Inc. ImmuKnow [website]. Columbia, MD: Cylex; 2008. Available at: <http://www.cylex.net/index.html>. Accessed August 5, 2010

Serban G, Whittaker V, Fan J, et al. Significance of immune cell function monitoring in renal transplantation after Thymoglobulin induction therapy. *Hum Immunol*. 2009;70(11):882-890.

Xue F, Zhang J, Han L, et al. Immune cell functional assay in monitoring of adult liver transplantation recipients with infection. *Transplantation*. 2010; 89(5):620-626.

Huskey J, Gralla J, Wiseman AC. Single time point immune function assay (ImmuKnow) testing does not aid in the prediction of future opportunistic infections or acute rejection. *Clin J Am Soc Nephrol*. 2011 Feb;6(2):423-9.

Rodrigo E, López-Hoyos M, Corral M, Fábrega E, Fernández-Fresnedo G, San Segundo D, Piñera C, Arias M ImmuKnow as a diagnostic tool for predicting infection and acute rejection in adult liver transplant recipients: a systematic review and meta-analysis. *Liver Transpl*. 2012 Oct;18(10):1245-53.

Ling X, Xiong J, Liang W, Schroder PM, Wu L, Ju W, Kong Y, Shang Y, Guo Z, He X. Can immune cell function assay identify patients at risk of infection or rejection? A meta-analysis. *Transplantation*. 2012 Apr 15;93(7):737-43

Ravaioli M, Neri F, Lazzarotto T, et al. Immunosuppression Modifications Based on an Immune Response Assay: Results of a Randomized, Controlled Trial. *Transplantation*. Aug 2015;99(8):1625-1632.

Zheng K, Zhang JP, Tan JM, et al. Lack of clinical significance of the ImmuKnow(TM)-Cylex assay for the detection of cellular immune function in patients with renal cell carcinoma. *Genet Mol Res*. 2015;14(3):11543-11550

Chon WJ, Brennan DC. Investigational methods in the diagnosis of acute renal allograft rejection. *UpToDate*

Ryan CM, Chaudhuri A, Concepcion W, Grimm PC. Immune cell function assay does not identify biopsy-proven pediatric renal allograft rejection or infection. *Pediatr Transplant*. 2014;18(5):446-452.

Ashokkumar C, Soltys K, Mazariegos G, et al. Predicting cellular rejection with a cell-based assay: Preclinical evaluation in children. *Transplantation*. 2017;101(1):131-140.

Ravaioli M, Neri F, Lazzarotto T, Bertuzzo VR, et al. Immunosuppression modifications based on an immune response assay: Results of a randomized, controlled trial. *Transplantation*. 2015;99(8):1625-1632.

Whitlam JB, Ling L, Skene A, et al. Diagnostic application of kidney allograft-derived absolute cell-free DNA levels during transplant dysfunction. *Am J Transplant*. 2019;19(4):1037-1049.

Huang E, Sethi S, Peng A, et al. Early clinical experience using donor-derived cell-free DNA to detect rejection in kidney transplant recipients. *Am J Transplant*. 2019;19(6):1663-1670.

Oellerich M, Shipkova M, Asendorf T, et al. Absolute quantification of donor-derived cell-free DNA as a marker of rejection and graft injury in kidney transplantation: Results from a prospective observational study. *Am J Transplant*. 2019 May 7

Khush KK, Patel J, Pinney S, et al. Noninvasive detection of graft injury after heart transplant using donor-derived cell-free DNA: A prospective multicenter study. *Am J Transplant*. 2019 Mar 5

Weston, M. W., Rinde-Hoffman, D., & Lopez-Cepero, M. Monitoring cell-mediated immunity during immunosuppression reduction in heart transplant recipients with severe systemic infections. *Clin Transplant*, 2020;34(3), e13809.

Qin T, Gu X-G, Jeong S-S, et al. Impact of EBV infection and immune function assay for lymphoproliferative disorder in pediatric patients after liver transplantation: A single-center experience. *Hepatobiliary Pancreat Dis Int*. 2020;19(1):3-11.

Xue, F., Gao, W., Qin, T., Wu, C., Luo, Y., et al. Immune cell function assays in the diagnosis of infection in pediatric liver transplantation: an open-labeled, two center prospective cohort study. *Translational pediatrics*, 2021;10(2), 333-343.

This policy will be revised as necessary and reviewed no less than annually.

Devised: 1/2010

Revised: 1/18 (added coding); 1/20 (add test reference names), 1/22 (cross-reference MP168)

Reviewed: 1/11, 1/12, 1/13, 1/14, 1/15, 1/16, 1/17, 1/19, 1/21,

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

Please be advised that the use of the logos, service marks or names of Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company on a marketing, press releases or any communication piece regarding the contents of this medical policy is strictly prohibited without the prior written consent of Geisinger Health Plan. Additionally, the above medical policy does not confer any endorsement by Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company regarding the medical service, medical device or medical lab test described under this medical policy.